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(54) Title: NOVEL PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(57) Abstract: The present invention provides polynucleotides and secreted proteins encoded by the polynucleotides. The proteins include a variety of fusion proteins, including fusions comprising a signal peptide selected from the group consisting of signal peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide. The invention further provides therapeutic and diagnostic methods utilizing the polynucleotides, polypeptides, and antagonists of the polypeptides.

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Description

NOVEL PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

BACKGROUND OF THE INVENTION

Within the field of genetic engineering, polynucleotides encoding proteins of interest have been identified and cloned by methods that require a detailed knowledge of the structure and/or function of the polynucleotide or the encoded protein. These methods include hybridization screening, polymerase chain reaction (PCR), and expression cloning.

With the more recent advent of large DNA sequence databases and the accompanying data analysis tools, identification of genes of interest is possible through the analysis of raw sequence data. Databases can be "mined" to locate sequences that resemble (are "homologous to") sequences of known function. Alignment of similar sequences can be used to place novel sequences within families of structurally similar sequences. These analytical tools can be combined with structural information obtained from, for example, X-ray crystallography to predict the higher order structure of a novel polypeptide. These analyses also facilitate prediction of polypeptide function. These recent technological advances have greatly increased the pace of gene discovery.

Genetic engineering has made available a number of genes and proteins of pharmaceutical or other economic importance. Such proteins include, for example, tissue plasminogen activator (t-PA) (U.S. Patent No. 4,766,075), coagulation factor VII (U.S. Patent No. 4,784,950), erythropoietin (U.S. Patent No. 4,703,008), platelet derived growth factor (U.S. Patent No. 4,889,919), and various industrial enzymes (e.g., U.S. Patents Nos. 5,965,384; 5,942,431; and 5,922,586).

Although estimates vary as to the amount of the human genome that has been identified to date, there remains a need in the art for further characterization of the human genome and the proteins encoded thereby. Previously unknown genes and proteins will be useful in the treatment and/or prevention of many human diseases, included diseases that have heretofore been refractory to treatment.

35 SUMMARY OF THE INVENTION

Within one aspect of the invention there is provided an isolated polypeptide comprising fifteen contiguous amino acid residues of a polypeptide as

shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422. Within one embodiment, the isolated polypeptide is from 15 to 2235 amino acid residues in length. Within another embodiment, the at least fifteen contiguous amino acid residues of SEO ID NO:M are operably linked via a peptide bond or polypeptide linker to a second polypeptide selected from the group consisting of maltose binding protein, an immunoglobulin constant region, a polyhistidine tag, and a peptide as shown in SEQ ID NO:423. Within another embodiment, the polypeptide comprises at least 30 contiguous residues of SEQ ID NO:M. Within a further embodiment, the polypeptide comprises at least 47 contiguous residues of SEQ ID NO:M. Within additional embodiments, the polypeptide is selected from the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 10, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 82, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 136, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 186, 202, 204, 206, 208, 210, 224, 230, 232, 234, 236, 240, 242, 250, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 310, 312, 314, 316, 322, 324, 328, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, and 420; the group consisting of polypeptides of SEO ID NOS: 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 20 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, and 420; the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 25 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, and 416; or the group consisting of polypeptides of SEQ ID NOS: 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 30 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, and 416.

Within a second aspect of the invention there is provided an isolated, mature protein encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NO:N, wherein N is an odd integer from 1 to 421. Within certain embodiments, N is 3, 5, 7, 9, 11, 15, 17, 23, 27, 41, 47, 53, 61, 65, 67, 69, 71, 81, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 135, 137, 139, 155,

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157, 161, 163, 165, 167, 173, 177, 179, 185, 201, 203, 205, 207, 209, 223, 229, 231, 233, 235, 239, 241, 249, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 309, 311, 313, 315, 321, 323, 327, 325, 335, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, 415, or 419; N is 3, 5, 7, 11, 15, 17, 23, 27, 41, 47, 53, 61, 65, 67, 69, 71, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 137, 139, 155, 157, 161, 163, 165, 167, 173, 177, 179, 201, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 321, 323, 325, 335, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, 415, or 419; N is 3, 5, 7, 11, 15, 17, 23, 27, 41, 47, 53, 65, 67, 69, 71, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 137, 139, 155, 157, 161, 163, 165, 167, 173, 177, 179, 201, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 321, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, or 415; or N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.

A third aspect of the invention provides isolated polynucleotides encoding the polypeptides disclosed above. Within certain embodiments of the invention the polynucleotides comprise a sequence of nucleotides as shown in SEQ ID NO:N, wherein N is an odd integer as defined above

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Within a fourth aspect of the invention there is provided an expression vector comprising the following operably linked elements: a transcription promoter; a DNA segment encoding a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422; and a transcription terminator. Within certain embodiments, M is 4, 6, 8, 10, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 82, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 136, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 186, 202, 204, 206, 208, 210, 224, 230, 232, 234, 236, 240, 242, 250, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 310, 312, 314, 316, 322, 324, 328, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, or 420; M is 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, or 420; M is 4, 6, 8, 12, 16, 18, 24, 28, 42,

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48, 54, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, or 416; or M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.

A fifth aspect of the invention provides a cultured cell comprising the expression vector disclosed above. The cultured cell can be used, *inter alia*, within a method of producing a polypeptide, the method comprising (a) culturing the cell under conditions whereby the sequence of nucleotides is expressed, and (b) recovering the polypeptide. The invention also provides a polypeptide produced by this method.

Within a sixth aspect of the ivention there is provided an isolated polynucleotide encoding a fusion protein, wherein the fusion protein comprises a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer as defined above, operably linked to a second polypeptide.

Within a seventh aspect of the invention there is provided an expression vector comprising the following operably linked elements: a transcription promoter; a DNA segment encoding a fusion protein as disclosed above; and a transcription terminator. The invention further provides a cultured cell comprising this expression vector, wherein the cell expresses the DNA segment and produces the encoded fusion protein. Also provided is a method of producing a protein comprising culturing the cell under conditions whereby the DNA segment is expressed, and recovering the second polypeptide. Within one embodiment the recovered second polypeptide is joined to a portion of a protein of SEQ ID NO: M, wherein M is an even integer as defined above.

Within a further aspect of the invention there is provided a computerreadable medium encoded with a data structure comprising SEQ ID NO:X, wherein X is an integer from 1 to 422.

Within an additional aspect of the invention there is provided an antibody that specifically binds to a protein selected from of the group consisting of SEQ ID NO:M, wherein M is an even integer as defined above.

These and other aspects of the invention will become evident upon reference to the following detailed description of the invention.

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DETAILED DESCRIPTION OF THE INVENTION

Prior to setting forth the invention in detail, it may be helpful to the understanding thereof to define the following terms:

The term "affinity tag" is used herein to denote a polypeptide segment that can be attached to a second polypeptide to provide for purification of the second polypeptide or provide sites for attachment of the second polypeptide to a substrate. In principal, any peptide or protein for which an antibody or other specific binding agent is available can be used as an affinity tag. Affinity tags include a poly-histidine tract, protein A (Nilsson et al., EMBO J. 4:1075, 1985; Nilsson et al., Methods Enzymol. 198:3, 1991), glutathione S transferase (Smith and Johnson, Gene 67:31, 1988), Glu-Glu affinity tag (Grussenmeyer et al., Proc. Natl. Acad. Sci. USA 82:7952-7954, 1985; see SEQ ID NO:423), substance P, Flag™ peptide (Hopp et al., Biotechnology 6:1204-1210, 1988), maltose binding protein (Kellerman and Ferenci, Methods Enzymol. 90:459-463, 1982; Guan et al., Gene 67:21-30, 1987), streptavidin binding peptide, 15 thioredoxin, ubiquitin, cellulose binding protein, T7 polymerase, immunoglobulin constant domain, or other antigenic epitope or binding domain. See, in general, Ford et al., Protein Expression and Purification 2: 95-107, 1991. Affinity tags can be used individually or in combination. DNAs encoding affinity tags and otehr reagents are available from commercial suppliers (e.g., Pharmacia Biotech, Piscataway, NJ; Eastman Kodak, New Haven, CT; New England Biolabs, Beverly, MA).

The term "allelic variant" is used herein to denote any of two or more alternative forms of a gene occupying the same chromosomal locus. Allelic variation arises naturally through mutation, and may result in phenotypic polymorphism within populations. Gene mutations can be silent (no change in the encoded polypeptide) or may encode polypeptides having altered amino acid sequence. The term allelic variant is also used herein to denote a protein encoded by an allelic variant of a gene.

The terms "amino-terminal" and "carboxyl-terminal" are used herein to denote positions within polypeptides. Where the context allows, these terms are used with reference to a particular sequence or portion of a polypeptide to denote proximity or relative position. For example, a certain sequence positioned carboxyl-terminal to a reference sequence within a polypeptide is located proximal to the carboxyl terminus of the reference sequence, but is not necessarily at the carboxyl terminus of the complete polypeptide.

A "complement" of a polynucleotide molecule is a polynucleotide 35 molecule having a complementary base sequence and reverse orientation as compared to a reference sequence. For example, the sequence 5' ATGCACGGG 3' is complementary to 5' CCCGTGCAT 3'.

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"Corresponding to", when used in reference to a nucleotide or amino acid sequence, indicates the position in a second sequence that aligns with the reference position when two sequences are optimally aligned.

The term "degenerate nucleotide sequence" denotes a sequence of nucleotides that includes one or more degenerate codons (as compared to a reference polynucleotide molecule that encodes a polypeptide). Degenerate codons encompass different triplets of nucleotides, but encode the same amino acid residue (i.e., GAU and GAC triplets each encode Asp).

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The term "expression vector" is used to denote a DNA molecule, linear or circular, that comprises a segment encoding a polypeptide of interest operably linked to additional segments that provide for its transcription, wherein said segments are arranged in a way that does not exist naturally. Such additional segments include promoter and terminator sequences, and may also include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors are generally derived from plasmid or viral DNA, or may contain elements of both.

The term "isolated", when applied to a polynucleotide, denotes that the polynucleotide has been removed from its natural genetic milieu and is thus free of other extraneous or unwanted coding sequences, and is in a form suitable for use within genetically engineered protein production systems. Such isolated molecules are those that are separated from their natural environment and include cDNA and genomic clones. Isolated DNA molecules of the present invention are free of other genes with which they are ordinarily associated, but may include naturally occurring 5' and 3' untranslated regions such as promoters and terminators. The identification of associated regions will be evident to one of ordinary skill in the art (see for example, Dynan and Tijan, *Nature* 316:774-78, 1985).

An "isolated" polypeptide or protein is a polypeptide or protein that is found in a condition other than its native environment, such as apart from blood and animal tissue. In a preferred form, the isolated polypeptide or protein is substantially free of other polypeptides or proteins, particularly other polypeptides or proteins of animal origin. It is preferred to provide the polypeptides or proteins in a highly purified form, i.e. greater than 95% pure, more preferably greater than 99% pure. When used in this context, the term "isolated" does not exclude the presence of the same polypeptide or protein in alternative physical forms, such as dimers or alternatively glycosylated or derivatized forms.

A "mature protein" is a protein that is produced by cellular processing of a primary translation product of a DNA sequence. Such processing may include

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removal of a secretory signal peptide, sometimes in combination with a propeptide. Mature sequences can be predicted from full-length sequences using methods known in the art for predicting cleavage sites. See, for example, von Heijne (Nuc. Acids Res. 14:4683, 1986). The sequence of a mature protein can be determined experimentally by expressing a DNA sequence of interest in a eukaryotic host cell and determining the amino acid sequence of the final product. For proteins lacking secretory peptides, the primary translation product will be the mature protein.

"Operably linked", when referring to DNA segments, indicates that the segments are arranged so that they function in concert for their intended purposes, e.g., transcription initiates in the promoter and proceeds through the coding segment to the terminator. When referring to polypeptides, "operably linked" includes both covalently (e.g., by disulfide bonding) and non-covalently (e.g., by hydrogen bonding, hydrophobic interactions, or salt-bridge interactions) linked sequences, wherein the desired function(s) of the sequences are retained.

The term "ortholog" denotes a polypeptide or protein obtained from one species that is the functional counterpart of a polypeptide or protein from a different species. Sequence differences among orthologs are the result of speciation.

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"Paralogs" are distinct but structurally related proteins made by an organism. Paralogs are believed to arise through gene duplication. For example, α -globin, β -globin, and myoglobin are paralogs of each other.

A "polynucleotide" is a single- or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases read from the 5' to the 3' end. Polynucleotides include RNA and DNA, and may be isolated from natural sources, synthesized *in vitro*, or prepared from a combination of natural and synthetic molecules. Sizes of polynucleotides are expressed as base pairs (abbreviated "bp"), nucleotides ("nt"), or kilobases ("kb"). Where the context allows, the latter two terms may describe polynucleotides that are single-stranded or double-stranded. When the term is applied to double-stranded molecules it is used to denote overall length and will be understood to be equivalent to the term "base pairs". It will be recognized by those skilled in the art that the two strands of a double-stranded polynucleotide may differ slightly in length and that the ends thereof may be staggered as a result of enzymatic cleavage; thus all nucleotides within a double-stranded polynucleotide molecule may not be paired. Such unpaired ends will in general not exceed 20 nt in length.

A "polypeptide" is a polymer of amino acid residues joined by peptide bonds, whether produced naturally or synthetically. Polypeptides of less than about 10 amino acid residues are commonly referred to as "peptides".

The term "promoter" is used herein for its art-recognized meaning to denote a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding regions of genes.

A "protein" is a macromolecule comprising one or more polypeptide chains. A protein may also comprise non-peptidic components, such as carbohydrate groups. Carbohydrates and other non-peptidic substituents may be added to a protein by the cell in which the protein is produced, and will vary with the type of cell. Proteins are defined herein in terms of their amino acid backbone structures; substituents such as carbohydrate groups are generally not specified, but may be present nonetheless.

A "secretory signal sequence" is a DNA sequence that encodes a polypeptide (a "secretory peptide") that, as a component of a larger polypeptide, directs the larger polypeptide through a secretory pathway of a cell in which it is synthesized. The larger polypeptide is commonly cleaved to remove the secretory peptide during transit through the secretory pathway.

The present invention is based in part upon the discovery of a group of novel, protein-enoding DNA molecules. These DNA molecules and the amino acid sequences that they encode are shown in SEQ ID NO:1 through SEQ ID NO:436.

20 Sequence analysis predicts that each of the encoded proteins includes an aminoterminal secretory peptide. These secretory peptides are shown below in Table 1, wherein residue numbers are in reference to the indicated SEQ ID NO. As will be understood by those skilled in the art, the cleavage sites predicted by conventional models of secretory peptide cleavage (e.g., von Heijne, Nuc. Acids Res. 14:4683, 1986)

25 are not always exact and may vary by as much as ± 5 residues. In addition, cleavage may occur at multiple sites within 5 residues of the indicated position. The mature form of any given protein may thus consists of a plurality of species differing at their amino termini.

Table 1

<u>Protein</u>	SEQ ID NO:	Residues 1-
AFP210015	2	14
AFP170681	4	26
AFP413680	6	28
AFP483037	8	14
AFP230872	10	27
AFP178828	12	14
AFP200134	14	23
AFP195796	16	22
AFP477303	18	18
AFP354334	20	25
AFP250287	22	17
AFP177000	24	26
AFP278176	26	21
AFP202885	28	18
AFP221312	30	23
AFP239757	32	22
AFP226311	34	20
AFP305901	36	20
AFP325549	38	20
AFP81988	40	. 14
AFP199200	42	20
AFP290395	44	23
AFP212675	46	20
AFP326051	48	17
AFP512441	50	18
AFP55098	52	15
AFP169796	54	21
AFP280706	56	25
AFP383165	58	23
AFP195467	60	26
AFP134225	62	22
AFP261193	64	28
AFP324422	66	28
AFP374312	68	28
AFP258118	70	24
AFP74517	72	25
AFP254653	74	18
AFP108666	76	21
AFP8766	78	15
AFP397185	80	20
AFP195042	82	21
AFP310695	84	26
AFP70022	86	19
AFP121670	88	22
AFP345861	90	15

AFP395942	92	16
AFP170291	94	21
AFP297548	96	22
AFP188135	98	28
AFP302388	100	19
AFP263430	102	17
AFP201273	104	18
AFP98983	106	25
AFP581958	108	20
AFP404202	110	19
AFP207203	112	15
AFP220790	114	19
AFP536326	116	23
AFP257473	118	22
AFP248380	120	16
AFP276202	122	20
AFP227568	124	23
AFP229039	126	20
AFP176297	128	17
AFP356885	130	17
AFP226938	132	16
AFP138504	134	29
AFP359196	136	24
AFP501809	138	27
AFP152733	140	15
AFP541394	142	23
AFP243183	144	20
AFP80739	146	18
AFP361806	148	26
AFP483930	150	21
AFP257336	152	25
AFP195800	154	23
AFP179530	156	19
AFP279267	158	14
AFP299766	160	29
AFP244615	162	16
AFP325761	164	22
AFP226024	166	22
AFP257094	168	27
AFP197103	170	27
AFP271855	172	17
AFP324816	174	29
AFP407963	176	25
AFP369635	178	17
AFP93743	180	28
AFP243230	182	15
AFP169316	184	21
AFP130852	186	15

AFP194191	188	22
AFP213472	190	21
AFP360430	192	22
AFP491309	194	21
AFP193428	196	23
AFP366534	198	22
AFP22706	200	27
AFP389012	202	14
AFP137186	204	24
AFP127023	206	21
AFP389687	208	16
AFP293220	210	25
AFP425535	212	25
AFP301494	214	25
AFP345421	216	19
AFP216667	218	26
AFP247951	220	29
AFP4464	222	22
AFP561930	224	28
AFP192851	226	22
AFP252759	228	20
AFP199044	230	20
AFP357958	232	28
AFP117501	234	15
AFP194554	236	23
AFP371069	238	23
AFP313600	240	19
AFP262739	242	18
AFP180730	244	27
AFP287227	246	28
AFP75785	248	26
AFP174843	250	15
AFP250422	252	15
AFP198645	254	17
AFP238111	256	16
AFP460626	258	24
AFP271081	260	14
AFP277752	262	16
AFP291338	264	15
AFP551038	266	22
AFP301579	268	20
AFP266188	270	16
AFP275580	272	28
AFP298054	274	21
AFP348226	276	23
AFP349106	278	23
AFP288248	280	15
AFP436476	282	19

AFP352125	284	14
AFP62060	286	25
AFP236718	288	21
AFP75775	290	25
AFP407487	292	23
AFP280451	294	27
AFP11675	296	29
AFP348656	298	16
AFP277451	300	19
AFP287436	302	14
AFP116043	304	28
AFP138740	306	26
AFP15192	308	17
AFP169968	310	27
AFP173341	312	23
AFP17588	314	23
AFP176427	316	20
AFP192633	318	14
AFP193013	320	15
AFP193881	322	16
AFP195562	324	16
AFP199922	326	18
AFP204736	328	17
AFP206179	330	27
AFP221877	332	23
AFP222758	334	26
AFP227032	336	24
AFP229269	338	27
AFP232213	340	25
AFP237679	342	21
AFP249599	344	28
AFP275215	346	21
AFP290397	348	26
AFP306591	350	18
AFP310297	352	20
AFP314720	354	19
AFP318671	356	29
AFP323575	358	21
AFP327160	360	20
AFP329002	362	29
AFP345415	364	24
AFP347179	366	24
AFP359138	368	23
AFP365372	370	17
AFP367284	372	23
AFP372822	374	26
AFP374595	376	29
AFP375952	378	25

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AFP382913	380	17
AFP389184	382	23
AFP404208	384	20
AFP404279	386	29
AFP409112	388	26
AFP413111	390	19
AFP415635	392	15
AFP421092	394	17
AFP436666	396	25
AFP448623	398	19
AFP454192	400	20
AFP49026	402	28
AFP51688	404	28
AFP525341	406	16
AFP545268	408	15
AFP592620	410	22
AFP62197	412	23
AFP68229	414	25
AFP71288	416	15

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AFP77851

AFP81957

AFP85168

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A secretory peptide of a protein of the present invention can be used to direct the secretion of other proteins of interest from a host cell. Thus, the present invention provides, inter alia, fusions comprising such a secretory peptide of a protein disclosed herein operably linked to another protein of interest. The secretory peptide can be used to direct the secretion of other proteins of interest by joining a polynucleotide sequence encoding it, in the correct reading frame, to the 5' end of a sequence encoding the other protein of interest. Those skilled in the art will recognize that the resulting fused sequence may encode additional residues of a protein of the present invention at the amino terminus of the protein to be secreted. In the extreme case, the fusion may comprise an entire protein of the present invention fused to the amino terminus of a second protein, whereby secretion of the fusion protein is directed by the secretory peptide of the protein of the present invention. It will often be desirable to include a proteolytic cleavage site between the protein of the present invention (or portion thereof) and the other protein of interest. polynucleotide sequences are then introduced into a host cell, which is cultured according to conventional methods. The protein of interest is then recovered from the culture media. Methods for introducing DNA into host cells, culturing the cells, and isolating recombinant proteins are known in the art. Representative methods are summarized below.

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Within certain embodiments of the invention, the protein is selected from those listed in Table 2. Within related embodiments of the invention, the polynucleotide is selected from polynucleotides encoding the proteins listed in Table 2, i.e., for a protein of SEQ ID NO:M, the polynucleotide is SEQ ID NO:M-1.

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Table 2

SEQ ID NO:	Protein	SEQ ID NO:	Protein
6	AFP413680	234	AFP117501
12	AFP178828	236	AFP194554
18	AFP477303	240	AFP313600
24	AFP177000	242	AFP262739
42	AFP199200	252	AFP250422
48	AFP326051	254	AFP198645
66	AFP324422	258	AFP460626
68	AFP374312	270	AFP266188
72	AFP74517	272	AFP275580
90	AFP345861	288	AFP236718
92	AFP395942	294	AFP280451
96 ·	AFP297548	300	AFP277451
98	AFP188135	306	AFP138740
110	AFP404202	324	AFP195562
134	AFP138504	338	AFP229269
138	AFP501809	342	AFP237679
156	AFP179530	344	AFP249599
158	AFP279267	348	AFP290397
162	AFP244615	350	AFP306591
164	AFP325761	366	AFP347179
174	AFP324816	374	AFP372822
180	AFP93743	378	AFP375952
204	AFP137186	386	AFP404279
206	AFP127023	396	AFP436666
210	AFP293220	398	AFP448623
224	AFP561930	408	AFP545268
230	AFP199044	416	AFP71288

Higher order structures of the proteins of the present invention can be predicted by computer analysis using available software (e.g., the Insight II® viewer and homology modeling tools available from MSI, San Diego, CA; and King and Sternberg, *Protein Sci.* 5:2298-310, 1996). In addition, analytical algorithms permit the identification of homologies between newly discovered proteins and known proteins. Such homologies are indicative of related biological functions.

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AFP254653 is 49% identical in sequence to human lysozyme C. Lysozyme C is a secreted bacteriolytic enzyme with similarity to the alphalactalbumins. Both are small alpha + beta proteins with six conserved cysteines forming a disulfide core comprising three disulfide bonds. AFP254653 may also exhibit bacteriolytic or other antimicrobial activity.

AFP581958 is 43% identical to wheat aluminum-induced protein, a member of the Bowman-Birk proteinase inhibitor family. All serine proteinases possess an exposed inhibitor loop that is stabilized by intermolecular interactions (usually disulfide bonds) between residues flanking the binding loop and the protein core. Interaction between inhibitor and enzyme produces a stable complex that disassociates very slowly, producing either an unaffected or a modified inhibitor that is cleaved at the scissile bond of the binding loop. AFP581958 may be a secreted serine proteinase.

AFP220790 is 42% identical to chicken lysozyme G, a bacteriolytic glycosyl hydrolase that hydrolizes peptidoglycan homopolymers of the prokaryote cell walls. AFP220790 may thus be a secreted bacteriolytic enzyme, and may exhibit other antimicrobial activity.

AFP271855 is 37% identical to bovine granulocyte peptide A precursor (antimicrobial BGP-A). Bovine and murine granulocyte peptide A precursor (also called antimicrobial BGP-A) are disclosed in WIPO publication WO 97/29765. Bovine GP-A was isolated from a bone marrow library (WO 97/29765). GP-A exhibits activity against Gram-positive and Gram-negative bacteria, fungi and viruses. AFP271855 may exhibit antimicrobial (including one or more of anti-bacterial, anti-fungal, and antiviral) activity.

AFP298054 is 24% identical to human T1/ST2 ligand. The T1 gene is also known as ST2, DER4, and Fit-1. It encodes a member of the interleukin-1 (IL-1) receptor family. It is transcribed in two forms, a soluble form and a membrane-bound form. The classical IL-1 ligands (IL-1α, IL-1β, and IL-1ra) do not bind T1. A putative ligand for T1 was disclosed in 1996 (Gayle et al., J. Biol. Chem. 227:5784-5789, 1996).

This protein binds T1 but is unable to initiate signal transduction by the membrane-bound form. The ligand is apparently a type I membrane protein. It has a predicted molecular weight (excluding the signal sequence and transmembrane domain) of about 22 kD, and has no sequence or hydrophobicity profile similarity to the beta-trefoil cytokines IL-1 or the FGFs. AFP298054 may be an antagonist that binds the receptor and regulates the activity of an as yet undiscovered IL-1 homolog.

Table 3 lists homologies between AFP sequences and sequences contained in the GenBank database, Derwent protein (PSP) or polynucleotide (PSN) databases, or Protein Identification Resource (PIR).

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Table 3

Accession Number & Description
Accession Number & Description
AE003823 (fly genomic)
AE003515 (fly genomic)
AF283518 (Mus musculus elongation factor sec)
AE003808 (fly genomic)
PSN_V61483
AE003708 (fly genomic)
AE003677 (fly genomic)
PIR_T41241 (yeast oxysterol-binding protein family)
AE003718 (fly genomic)
AF113691 (human clone FLB4739 PRO1238 mRNA)
AC069237 (human chromosome 3 clone RP11-175M9)
AF247177 (Mus musculus sphingosine-1-phosphate
phosphohydrolase)
AF150741 (Rattus norvegicus prolactin-like protein J mRNA)
AE003559 (fly genomic)
AE003499 (fly genomic) Z1041035F6P
AF283518 (Mus musculus elongation factor sec mRNA)
AE003530 (fly genomic)
AE003538 (fly genomic)
AE003831 (fly genomic)
AB041564 (mouse brain cDNA; clone MNCb-0914)
AL137255 (human mRNA; cDNA DKFZp434B1813)
X14971 (mouse mRNA for alpha-adaptin, MMADAPA1)
AE003778 (fly genomic)
PSP_Y94938 (Human secreted protein clone ye78_1)
AL161655 (human chromosome 20 clone RP11-116E13)
PIR_T16263 (C. elegans hypothetical protein F35D11.3)

Table 4 lists AFP proteins for which regions of identity have been found in the GenBank database.

Table 4

Locus	Accession Number & Description
AFP127023	SK000740 (human cDNA FLJ20733; clone HEP08550; by homology: molybdopterin cofactor sulfurase)
AFP134225	AB020970 (human mRNA; partial cds and 3'UTR; up-regulated by BCG-CWS)
AFP195562	AK000382 (human cDNA FLJ20375; clone HUV00942)

AFP199044	HSU80813 (human nucleoside diphosphate kinase homolog DR-nm23)
AFP227032	AK001848 (human cDNA FLJ10986; clone PLACE1001869; weakly
	similar to L-RIBULOKINASE, EC 2.7.1.16)
AFP237679	AB000465 (human mRNA; exon 1; 2; 3; 4; clone: RES4-24B; in
	genomic region of Huntington's disease locus)
AFP262739	AK000135 (human cDNA FLJ20128; clone COL06181)
AFP369635	PSN_Z24827 (Human secreted protein gene 17 clone HNFIY77)
AFP81957	AF267730 (human 26S proteasome-associated UCH interacting protein
	1; UIP1)
AFP93743	AK000066 (human cDNA FLJ20059; clone COL01349)

Table 5 lists AFP proteins for which longer regions of identity have been found in proteins contained in GenBank and other databases.

Table 5

	Table 3
Locus	Accession Number & Description
AFP117501	AK000505 (human cDNA FLJ20498; clone KAT08960)
AFP138740	HSM802370 (human mRNA; cDNA DKFZp434M1511)
AFP170291	AK000494 (human cDNA FLJ20487; clone KAT08245)
AFP170681	AK001698 (human cDNA FLJ10836; clone NT2RP4001228 close
	paralogue of human Kelch-like 1 protein (KLHL1) mRNA: AF252283)
AFP177000	AK000524 (human cDNA FLJ20517; clone KAT10235)
AFP193881	AK000382 (human cDNA FLJ20375; clone HUV00942)
AFP195796	AF251041 (human SGC32445 protein (SGC32445) mRNA; homology
	to PSP_W35393 Human TB2 gene product)
AFP202885	AB037808 (human mRNA for KIAA1387 protein)
AFP207203	AF250924 (human PNGase mRNA: peptide N-glycanase)
AFP226024	AK001952 (human cDNA FLJ11090; clone PLACE1005308)
AFP227568	AB019038 (human HMT-1 mRNA for beta-1;4 mannosyltransferase)
AFP244615	AK001009 (human cDNA FLJ10147; clone HEMBA1003369; weak
	homology: CENE_HUMAN CENTROMERIC PROTEIN E)
AFP250422	AF208849 (human BM-007 mRNA)
AFP266188	AK000272 (human cDNA FLJ20265; clone COLF9334; homology to
	major facilitator protein homolog, fission yeast: PIR_S62432)
AFP277451	AK001373 (human cDNA FLJ10511; clone NT2RP2000656)
AFP277752	AK000453 (human cDNA FLJ20446; clone KAT05231; weak
	homology to dinitrogenase reductase activating glycohydrolase (draG)
	Archaeoglobus fulgidus: PIR_C69465)
AFP280451	AL133355 (Human DNA sequence from clone RP11-541N10 on
	chromosome 10. Contains a novel gene and the 5' end of the gene for a
	novel protein; ortholog of mouse FISH protein)
AFP293220	AK001441 (human cDNA FLJ10579; clone NT2RP2003446)
AFP297548	AK000494 (human cDNA FLJ20487; clone KAT08245)
AFP306591	AL359700 (human chromosome 6 clone RP11-802L12)
AFP324816	AB032966 (human mRNA for KIAA1140 protein weak homology:
	Human O-linked GlcNAc transferase mRNA)

AFP356885	AK001544 (human cDNA FLJ10682; clone NT2RP3000072)
AFP389012	AK000428 (human cDNA FLJ20421; clone KAT02467; homologus to
	human bisphosphate 3'-nucleotidase mRNA: AF125042)
AFP436666	AK001608 (human cDNA FLJ10746; clone NT2RP3001679; likely
	human orthologue of Rattus norvegicus small rec (srec) mRNA:
	AF228917)
AFP501809	AK001963 (human cDNA FLJ11101; clone PLACE1005623)
AFP525341	AF189692 (human non-kinase Cdc42 effector protein SPEC2 mRNA)

A protein of the present invention can be prepared as a fusion protein by joining it to a second polypeptide or a plurality of additional polypeptides. Suitable second polypeptides include amino- or carboxyl-terminal extensions, such as linker peptides of up to about 20-25 residues and extensions that facilitate purification (affinity tags) as disclosed above. A protein of interest can be prepared as a fusion to a dimerizing protein as disclosed in U.S. Patents Nos. 5,155,027 and 5,567,584. Preferred dimerizing proteins in this regard include immunoglobulin constant region domains. Immunoglobulin-polypeptide fusions can be expressed in genetically engineered cells to produce a variety of multimeric analogs of a protein of interest. Fusion proteins can also comprise auxiliary domains that target the protein of interest to specific cells, tissues, or macromolecules (e.g., collagen). For example, a protein of interest can be targeted to a predetermined cell type by fusing it to a ligand that specifically binds to a receptor on the surface of a target cell. In this way, proteins can be targeted for therapeutic or diagnostic purposes. A protein can be fused to two or more moieties, such as an affinity tag for purification and a targeting domain. Protein fusions can also comprise one or more cleavage sites, particularly between domains. See, Tuan et al., Connective Tissue Research 34:1-9, 1996. Proteins of the present invention can also be used as targetting moieties within fusion proteins comprising, for example, cytokines, cytotoxins, or other biologically active polypeptide moieties.

Protein fusions of the present invention will usually contain not more than about 1,200 amino acid residues joined to the AFP protein. For example, an AFP protein can be fused to $E.\ coli\ \beta$ -galactosidase (1,021 residues; see Casadaban et al., $J.\ Bacteriol.\ \underline{143}$:971-980, 1980), a 10-residue spacer, and a 4-residue factor Xa cleavage site. Such a protein comprising, for example, AFP345421 (SEQ ID NO:216), contains 2235 amino acid residues. In a second example, an AFP protein can be fused to maltose binding protein (approximately 370 residues), a 4-residue cleavage site, and a 6-residue polyhistidine tag.

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As disclosed above, the proteins of the present invention or portions thereof can also be used to direct the secretion of a second protein. When such fusions

are designed so that the secreted protein retains a portion of the protein of the present invention, the fusion protein can be purified by means that exploit the properties of the protein of the present invention. Typical of such methods is immunoaffinity chromatography using an antibody directed against a protein of the present invention. When such a fusion is engineered to contain a cleavage site at the fusion point, the fusion can be cleaved and the protein of interest recovered free of extraneous sequence.

The present invention also provides polynucleotide molecules, including DNA and RNA molecules, that encode the proteins disclosed above. Those skilled in the art will readily recognize that, in view of the degeneracy of the genetic code, considerable sequence variation is possible among these polynucleotide molecules. The amino acid sequence information provided herein can be used by one of ordinary skill in the art to generate degenerate sequences comprising all nucleotide sequences encoding a particular polypeptide. Table 6 sets forth the one-letter codes used to denote degenerate nucleotide positions. "Resolutions" are the nucleotides denoted by a code letter. "Complement" indicates the code for the complementary nucleotide(s). For example, the code Y denotes either C or T, and its complement R denotes A or G, A being complementary to T, and G being complementary to C.

TABLE 6

20 Nucleotide Resolutions Complement Resolutions Α Α T $\overline{\mathbf{T}}$ \mathbf{C} C G G G G · C C T T A Α R AG Y C|T CIT Y R AG M A|C K GIT K **G**|T AIC M S CIG S C|G W A|T A|TW A|C|T A|G|T H D CIGIT В V AICIG V A|C|G CGT В D A|G|T A|C|T H N A|C|G|T AICIGIT N

Degenerate codons encompassing all possible codons for a given amino acid are set forth in Table 7, below.

TABLE 7

Amino	One-Letter		Degenerate
Acid	Code	Codons	Codon
Cys	C	TGC TGT	TGY
Ser	S	AGC AGT TCA TCC TCG TCT	WSN
Thr	T	ACA ACC ACG ACT	CAN
Pro	P	CCA CCC CCG CCT	CCN
Ala	Α	GCA GCC GCG GCT	GCN
Gly	G	GGA GGC GGG GGT	GGN
Asn	N	AAC AAT	AAY
Asp	D	GAC GAT	GAY
Glu	E	GAA GAG	GAR
Gln	Q	CAA CAG	CAR
His	Н	CAC CAT	CAY
Arg	R	AGA AGG CGA CGC CGG CGT	MGN
Lys	K .	AAA AAG	AAR
Met	M	ATG	ATG
Ile	I	ATA ATC ATT	ATH
Leu	L	CTA CTC CTG CTT TTA TTG	YTN
Val	V	GTA GTC GTG GTT	GTN
Phe	F	TTCTTT	TTY
Tyr	Y	TAC TAT	TAY
Trp	w	TGG	TGG
Ter		TAA TAG TGA	TRR •
Asn Asp	В		RAY
Glu Gln	Z		SAR
Any	X		NNN
Gap	-		

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One of ordinary skill in the art will appreciate that some ambiguity is introduced in determining a degenerate codon, representative of all possible codons encoding each amino acid. For example, the degenerate codon for serine (WSN) can, in some circumstances, encode arginine (AGR), and the degenerate codon for arginine (MGN) can, in some circumstances, encode serine (AGY). A similar relationship

exists between codons encoding phenylalanine and leucine. Thus, some polynucleotides encompassed by the degenerate sequences may encode variant amino acid sequences, but one of ordinary skill in the art can easily identify such variant sequences by reference to the amino acid sequences disclosed in the accompanying Sequence Listing.

Methods for preparing DNA and RNA are well known in the art. Complementary DNA (cDNA) clones are prepared from RNA that is isolated from a tissue or cell that produces large amounts of the cognate mRNA. Such tissues and cells are identified by methods commonly known in the art, such as Northern blotting (Thomas, *Proc. Natl. Acad. Sci. USA* 77:5201, 1980). Databases of expressed sequence tags (ESTs) can be analyzed to produce an "electronic Northern" wherein sequences are assigned to specific cell or tissue sources on the basis of their abundance within libraries. Table 8, below, shows the results of such an analysis when, as the minimum significant abundance, it was required that at least 10% of all sequences for a given protein were from a single source and at least five individual clones had been identified from that source. Sequences shown in the accompanying Sequence Listing but not listed in Table 8 were widely distributed among various tissues or were represented by few clones.

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Table 8

AFP152733	K562 cells
AFP169796	T-cells
AFP173341	testis
AFP17588	fetal liver or spleen
AFP194554	fetal liver or spleen
AFP199922	testis
AFP229269	placenta
AFP237679	fetal liver or spleen
AFP257094	adult brain
AFP258118	epidermal breast keratinocytes
AFP263430	breast
AFP276202	infant brain
AFP287436	testis
AFP290397	testis
AFP306591	fetal heart
AFP325761	K562 cells
AFP352125	testis
AFP359138	infant brain
AFP369635	germinal center B-cells
AFP409112	kidney
AFP483037	neonatal keratinocytes
AFP49026	peripheral blood eosinophils of asthma patients
AFP545268	K562 cells
AFP561930	fetal liver or spleen
AFP62060	testis
AFP62197	pregnant uterus
AFP93743	germinal center B-cells
AFP98983	fetal heart

A panel of cDNAs from human tissues was screened for AFP expression using PCR. The panel was made from first strand cDNAs obtained from Clontech laboratories, Inc., Palo Alto, CA and contained 20 first-strand cDNA samples from the human tissues shown in Table 9. The panel was set up in a 96-well format that further included a human genomic DNA (obtained from Clontech Laboratories, Inc.) positive control sample and a water-only well as a negative control sample. Each well contained approximately 0.2-100 pg/µl of cDNA, diluted with water to 17.5µl. The

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PCR reactions were set up by adding oligonucleotide primers, DNA polymerase (Ex TaqTM; TAKARA Shuzo Co. Ltd. Biomedicals Group, Japan or AdvantageTM 2 cDNA polymerase mix; Clontech Laboratories, Inc.) with the appropriate supplied buffer, dNTP mix (TAKARA Shuzo Co. Ltd.), and a density increasing agent and tracking dye (RediLoad; Research Genetics, Inc., Huntsville, AL) to each sample on the panel. The amplification was carried out as follows: incubation at 94°C for 2 minutes; 35 cycles of 94°C for 30 seconds, 60°C for 20 seconds, and 72°C for 30 seconds; followed by incubation at 72°C for 5 minutes. About 10 μl of the PCR reaction product was subjected to standard agarose gel electrophoresis using a 4% agarose gel.

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	20	^	^	>	_	>	_	>	_	у	λ	у	c	E	^	ý	У	у	y	u	y	у	y	y	у	У	у	y	y	у	Z	У	ď
	61	^	c	_	>	×	^	_	^	y	^	У	L	E	^	y	y	y	y	u	у	y	y	y	y	y	у	y	у	y	Ž	y	×
	18	×	×	y	_	y	^	_	\ \	y	y	y	u	e e	_	y	y	y	y	c	y	y	У	y	y	y	y	λ	y	y	^	,	_
	12	y	γ	y	_	V	y	>	^	×	×	y	u	_	_	, ,	Г	y	y	u	y	П	V	u	u	y	<u>۷</u>	×	y	у	ng E	,	
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Table	12	y	γ	λ	^	y	y	y	,	ý	у	y	u	u	Ý	у	u	Jy	y	u	y	y	λ	У	ý	y	y	y	y	у	λ	×	
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	2	y	у	у	^	ý	y	у	у	y	у	у	u	u	y	y	γ	y	y	c	λ	Λ	Λ	У	γ	y	y	y	y	у	Υ	^	<u>-</u>
	6	y	y	y	y	,	y	y	y	ý	u	λ	u	u	y	y	u	y	ý	u	y	^	`	y	y	E	y	y	y	y	Λ	^	E
	∞	y	y	y	у	ý	y	ý	y .	y	y	y	c	u	y	y	u	У	y	У	y	λ	^	Ľ	γ	Υ	λ	γ	λ,	У	λ	^	_
	7	y	λ	у	у	ý	y	y	λ	ý	y	y	u	u	ý	l y	y	y	y	у	λ	y	У	У	у	y	y	y	y	y	λ	Ż	c
	9	y	у	у	y	y	y	y	У	λ	y	γ	c	c	γ	^	γ	γ	>	у	y	λ	>	λ	у	χ	*	λ	y	λ	>	^	=
	2	y	χ	y	y	λ	у	γ	γ	λ	γ	γ	c	c	y	y	γ	λ	_	E .	γ	χ	^	y	У	У	у	у	У	У	У	χ	_
	4	У	y	y	λ	У	У	У	У	λ	У	У	u	у	y	γ	У	У	λ	u	у	7	χ	У	y	y	y	y	y	^	>	7	_
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	7	y	Ż	Ż	y	λ	y	y	y	ý	y	^	c	u	λ	^	ý	^	^	y	^	λ	^	y	λ	'n	ý	У	^	_	7	>	c
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	ein	AFP117501	AFP127023	AFP137186	AFP138504	AFP138740	AFP177000	AFP178828	179530	AFP188135	AFP194554	AFP195562	AFP198645	AFP199044	AFP199200	AFP229269	AFP236718	AFP237679	AFP244615	AFP249599	AFP250422	AFP262739	AFP266188	AFP275580	AFP277451	AFP279267	AFP280451	AFP290397	AFP293220	AFP297548	AFP306591	AFP313600	AFP324422
	Protein	AFP	AFF	AFP	AFF	AFP	AFP	AFP	AFP	AFF	AFP	Ā	AFP	AFP																			

Table 9, continued

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	20	y	y	y	y	y	y	u	u	y	y	y	y	y	c	y	y	y	y	y	u	γ	
	19	У	У	У	γ	λ	λ	u	u	У	У	λ	У	y	у	λ	λ	У	у	pu	c	γ	
	18	У	У	У	у	У	У	У	n	У	у	У	У	У	У	У	У	у	у	у.	c	y	
	17	у	y	y	у	c.	у	у	n	y	y	u	pu	У	c	pu	у	y	y	y	u	y	
	91	y	y	y	у	y	y	u	u	y	y	y	y	y	u	y	y	y	y	y	u	y	
	15	y	y	y	у	у	У	u	u	u	y	y	y	у	у	y	у	y	y	y	u	y	
	14	y	y	y	pu	y	У	u				y					П			pu	u	y	
	13	y	u	y			y	u				y								_		Н	ŀ
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Tissues screened were: 1, brain; 2, heart; 3, kidney; 4, liver; 5, lung; 6, pancreas; 7, placenta; 8, skeletal muscle; 9, colon; 10, ovary; 11, peripheral blood leukocytes; 12, prostate; 13, small intestine; 14, spleen; 15, testis; 16, thymus; 17, bone marrow; 18, fetal liver; 19, lymph node; 20, tonsil; 21, H₂O; 22, genomic DNA. Y=yes; n=no; nd=not determined.

Total RNA can be prepared using guanidine HCl extraction followed by isolation by centrifugation in a CsCl gradient (Chirgwin et al., *Biochemistry* 18:52-94, 1979). Poly (A)+ RNA is prepared from total RNA using the method of Aviv and Leder (*Proc. Natl. Acad. Sci. USA* 69:1408-1412, 1972). Complementary DNA (cDNA) is prepared from poly(A)+ RNA using known methods. In the alternative, genomic DNA can be isolated. For some applications (e.g., expression in transgenic animals) it may be preferable to use a genomic clone, or to modify a cDNA clone to include at least one genomic intron. Methods for identifying and isolating cDNA and genomic clones are well known and within the level of ordinary skill in the art, and include the use of the sequences disclosed herein, sequences complementary thereto, or parts thereof, for probing or priming a library. Such methods include, for example, hybridization or polymerase chain reaction ("PCR", Mullis, U.S. Patent 4,683,202). Expression libraries can be probed with antibodies to a protein of interest, receptor fragments, or other specific binding partners.

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The polynucleotides of the present invention can also be prepared by automated synthesis. Synthesis of polynucleotides is within the level of ordinary skill in the art, and suitable equipment and reagents are available from commercial suppliers. See, in general, Glick and Pasternak, Molecular Biotechnology, Principles & Applications of Recombinant DNA, ASM Press, Washington, D.C., 1994; Itakura et al., Ann. Rev. Biochem. 53: 323-56, 1984; and Climie et al., Proc. Natl. Acad. Sci. USA 87:633-7, 1990.

The present invention further provides antisense polynucleotides that are complementary to a segment of a polynucleotide as set forth in one of SEQ ID NO:N, wherein N is an odd integer from 1 to 435. Such antisense polynucleotides are designed to bind to the corresponding mRNA and inhibit its translation. Antisense polynucleotides are used to inhibit gene expression in cell culture or in a patient, and can be used as probes or primers for research or diagnostic purposes.

Probes and primers of the present invention comprise a suitable fragment, and may comprise up to the complete sequence, of a polynucleotide as shown in SEQ ID NO:N or the complement thereof, wherein N is an odd integer from 1 to 421. Probes will generally be at least 20 nucleotides in length, although somewhat shorter probes (14-17 nucleotides) can be used. PCR primers are at least 5 nucleotides in length, preferably 15 or more nt, more preferably 20-30 nt. Shorter polynucleotide probes and primers are referred to in the art as "oligonucleotides," and can be DNA or RNA. Probes will generally comprise an oligonucleotide linked to a label, such as a radionuclide.

Probes and primers as disclosed herein can be used for cloning allelic, orthologous, and paralogous sequences. Allelic variants of the disclosed sequences can be cloned by probing cDNA or genomic libraries from different individuals according to standard procedures. Orthologous sequences can be cloned using information and compositions provided by the present invention in combination with conventional cloning techniques. For example, a cDNA can be cloned using mRNA obtained from a tissue or cell type that expresses the protein. Suitable sources of mRNA can be identified by probing Northern blots with probes designed from the sequences disclosed herein. A library is then prepared from mRNA of a positive tissue or cell line. A cDNA can then be isolated by a variety of methods, such as by probing with a complete or partial human cDNA or with one or more sets of degenerate probes based on the disclosed sequences. A cDNA can also be cloned by PCR using primers designed from the sequences disclosed herein. Within an additional method, the cDNA library can be used to transform or transfect host cells, and expression of the cDNA of interest can be detected with an antibody to the encoded protein. Similar techniques can also be applied to the isolation of genomic clones. Orthologous and paralogous sequences can be identified from libraries by probing blots at low stringency and washing the blots at successively higher stringency until background is suitably reduced.

Probes and primers disclosed herein can be used to clone 5' non-coding regions of a corresponding gene. In view of the tissue-specific expression observed for certain proteins of the invention (Tables 8 and 9), promoters of these genes are expected to provide tissue-specific expression. Such promoter elements can thus be used to direct the tissue-specific expression of heterologous genes in, for example, transgenic animals or patients treated with gene therapy. Cloning of 5' flanking sequences also facilitates production of a protein of interest by "gene activation" as disclosed in U.S. Patent No. 5,641,670. Briefly, expression of an endogenous gene in a cell is altered by introducing into its locus a DNA construct comprising at least a targeting sequence, a regulatory sequence, an exon, and an unpaired splice donor site. The targeting sequence is a 5' non-coding sequence that permits homologous recombination of the construct with the endogenous locus, whereby the sequences within the construct become operably linked with the endogenous coding sequence. In this way, an endogenous promoter can be replaced or supplemented with other regulatory sequences to provide enhanced, tissue-specific, or otherwise regulated expression.

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The polynucleotides of the present invention further include polynucleotides encoding the fusion proteins, including signal peptide fusions, disclosed above.

The present invention further provides a computer-readable medium encoded with a data structure that provides at least one of SEQ ID NO:1 through SEQ ID NO:436. Suitable forms of computer-readable media include magnetic media and optically-readable media. Examples of magnetic media include a hard or fixed drive, a random access memory (RAM) chip, a floppy disk, digital linear tape (DLT), a disk cache, and a ZIP® disk. Optically readable media are exemplified by compact discs (e.g., CD-read only memory (ROM), CD-rewritable (RW), and CD-recordable),digital versatile/video discs (DVD) (e.g., DVD-ROM, DVD-RAM, and DVD+RW), and carrier waves.

The polypeptides of the present invention, including full-length proteins, biologically active fragments, immunogenic fragments, and fusion proteins, can be produced in genetically engineered host cells according to conventional techniques. Suitable host cells are those cell types that can be transformed or transfected with exogenous DNA and grown in culture, and include bacteria, fungal cells, and cultured higher eukaryotic cells. Eukaryotic cells, particularly cultured cells of multicellular organisms, are generally preferred for the production of proteins having higher eukaryotic-type post-translational modifications (e.g., γ-carboxylation) and for making proteins, especially secretory proteins, for pharmaceutical use in humans. Techniques for manipulating cloned DNA molecules and introducing exogenous DNA into a variety of host cells are disclosed by Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989, and Ausubel et al., eds., *Current Protocols in Molecular Biology*, Green and Wiley and Sons, NY, 1993.

In general, a DNA sequence encoding a polypeptide of interest is operably linked to other genetic elements required for its expression, generally including a transcription promoter and terminator, within an expression vector. The vector will also commonly contain one or more selectable markers and one or more origins of replication, although those skilled in the art will recognize that within certain systems selectable markers can be provided on separate vectors, and replication of the exogenous DNA can be achieved through integration into the host cell genome. Selection of promoters, terminators, selectable markers, vectors and other elements is a matter of routine design within the level of ordinary skill in the art. Many such elements are described in the literature and are available through commercial suppliers.

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To direct a polypeptide into the secretory pathway of a host cell, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) is provided in the expression vector. The secretory signal sequence may be that of the protein of interest, or may be derived from another secreted protein (e.g., t-PA; see U.S. Patent No. 5,641,655) or synthesized *de novo*. The secretory signal sequence is operably linked to the DNA sequence encoding the protein of interest, i.e., the two sequences are joined in the correct reading frame and positioned to direct the newly synthesized protein into the secretory pathway of the host cell. Secretory signal sequences are commonly positioned 5' to the DNA sequence encoding the protein of interest, although certain secretory signal sequences may be positioned elsewhere in the DNA sequence of interest (see, e.g., Welch et al., U.S. Patent No. 5,037,743; Holland et al., U.S. Patent No. 5,143,830).

Cultured mammalian cells are suitable hosts for use within the present invention. Methods for introducing exogenous DNA into mammalian host cells 15 include calcium phosphate-mediated transfection (Wigler et al., Cell 14:725, 1978; Corsaro and Pearson, Somatic Cell Genetics 7:603, 1981: Graham and Van der Eb, Virology 52:456, 1973), electroporation (Neumann et al., EMBO J. 1:841-845, 1982), DEAE-dextran mediated transfection (Ausubel et al., ibid.), and liposome-mediated transfection (Hawley-Nelson et al., Focus 15:73, 1993; Ciccarone et al., Focus 15:80, 1993). The production of recombinant polypeptides in cultured mammalian cells is 20 disclosed by, for example, Levinson et al., U.S. Patent No. 4,713,339; Hagen et al., U.S. Patent No. 4,784,950; Palmiter et al., U.S. Patent No. 4,579,821; and Ringold, U.S. Patent No. 4,656,134. Suitable cultured mammalian cells include the COS-1 (ATCC No. CRL 1650), COS-7 (ATCC No. CRL 1651), BHK (ATCC No. CRL 25 1632), BHK 570 (ATCC No. CRL 10314), 293 (ATCC No. CRL 1573; Graham et al., J. Gen. Virol. 36:59-72, 1977) and Chinese hamster ovary (e.g. CHO-K1; ATCC No. CCL 61) cell lines. Additional suitable cell lines are known in the art and available from public depositories such as the American Type Culture Collection, Rockville, Maryland. In general, strong transcription promoters are preferred, such as promoters 30 from SV-40 or cytomegalovirus. See, e.g., U.S. Patent No. 4,956,288. Other suitable promoters include those from metallothionein genes (U.S. Patent Nos. 4,579,821 and 4,601,978) and the adenovirus major late promoter. Within an alternative embodiment, adenovirus vectors can be employed. See, for example, Garnier et al., Cytotechnol. 15:145-55, 1994.

Drug selection is generally used to select for cultured mammalian cells into which foreign DNA has been inserted. Such cells are commonly referred to as "transfectants". Cells that have been cultured in the presence of the selective agent and

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are able to pass the gene of interest to their progeny are referred to as "stable transfectants." An exemplary selectable marker is a gene encoding resistance to the antibiotic neomycin. Selection is carried out in the presence of a neomycin-type drug, such as G-418 or the like. Selection systems can also be used to increase the expression level of the gene of interest, a process referred to as "amplification." Amplification is carried out by culturing transfectants in the presence of a low level of the selective agent and then increasing the amount of selective agent to select for cells that produce high levels of the products of the introduced genes. An exemplary amplifiable selectable marker is dihydrofolate reductase, which confers resistance to methotrexate. Other drug resistance genes (e.g. hygromycin resistance, multi-drug resistance, puromycin acetyltransferase) can also be used.

Insect cells can be infected with recombinant baculovirus, commonly derived from *Autographa californica* nuclear polyhedrosis virus (AcNPV). See, King and Possee, The Baculovirus Expression System: A Laboratory Guide, London, Chapman & Hall; O'Reilly et al., Baculovirus Expression Vectors: A Laboratory Manual, New York, Oxford University Press., 1994; and Richardson, Ed., Baculovirus Expression Protocols. Methods in Molecular Biology, Humana Press, Totowa, NJ, 1995. Recombinant baculovirus can also be produced through the use of a transposon-based system described by Luckow et al. (*J. Virol.* 67:4566-4579, 1993). This system, which utilizes transfer vectors, is commercially available in kit form (Bac-to-Bac™ kit; Life Technologies, Rockville, MD). See also, Hill-Perkins and Possee, *J. Gen. Virol.* 71:971-976, 1990; Bonning et al., *J. Gen. Virol.* 75:1551-1556, 1994; and Chazenbalk and Rapoport, *J. Biol. Chem.* 270:1543-1549, 1995.

For protein production, the recombinant virus is used to infect host cells, typically a cell line derived from the fall armyworm, Spodoptera frugiperda (e.g., Sf9 or Sf21 cells) or Trichoplusia ni (e.g., High Five™ cells; Invitrogen, Carlsbad, CA). See, in general, Glick and Pasternak, Molecular Biotechnology: Principles and Applications of Recombinant DNA, ASM Press, Washington, D.C., 1994. See also, U.S. Patent No. 5,300,435. Serum-free media are used to grow and maintain the cells. Suitable media formulations are known in the art and can be obtained from commercial suppliers. The cells are grown up from an inoculation density of approximately 2-5 x 10⁵ cells to a density of 1-2 x 10⁶ cells, at which time a recombinant viral stock is added at a multiplicity of infection (MOI) of 0.1 to 10, more typically near 3. Procedures used are generally described in available laboratory manuals (e.g., King and Possee, ibid.; O'Reilly et al., ibid.; Richardson, ibid.). See also, Guarino et al., U.S. Patent No. 5,162,222 and WIPO publication WO 94/06463.

Fungal cells, including yeast cells, can also be used within the present invention. Yeast species of particular interest in this regard include Saccharomyces cerevisiae, Pichia pastoris, and Pichia methanolica. Methods for transforming S. cerevisiae cells with exogenous DNA and producing recombinant polypeptides therefrom are disclosed by, for example, Kawasaki, U.S. Patent No. 4,599,311; Kawasaki et al., U.S. Patent No. 4,931,373; Brake, U.S. Patent No. 4,870,008; Welch et al., U.S. Patent No. 5,037,743; and Murray et al., U.S. Patent No. 4,845,075. Transformed cells are selected by phenotype determined by the selectable marker, commonly drug resistance or the ability to grow in the absence of a particular nutrient (e.g., leucine). A preferred vector system for use in Saccharomyces cerevisiae is the POT1 vector system disclosed by Kawasaki et al. (U.S. Patent No. 4,931,373), which allows transformed cells to be selected by growth in glucose-containing media. Suitable promoters and terminators for use in yeast include those from glycolytic enzyme genes (see, e.g., Kawasaki, U.S. Patent No. 4,599,311; Kingsman et al., U.S. 15 Patent No. 4,615,974; and Bitter, U.S. Patent No. 4,977,092) and alcohol dehydrogenase genes. See also U.S. Patents Nos. 4,990,446; 5,063,154; 5,139,936 and 4,661,454.

Transformation systems for other yeasts, including Hansenula polymorpha, Schizosaccharomyces pombe, Kluyveromyces lactis, Kluyveromyces 20 fragilis, Ustilago maydis, Pichia pastoris, Pichia methanolica, Pichia guillermondii and Candida maltosa are known in the art. See, for example, Gleeson et al., J. Gen. Microbiol. 132:3459-3465, 1986 and Cregg, U.S. Patent No. 4,882,279. Aspergillus cells may be utilized according to the methods of McKnight et al., U.S. Patent No. 4,935,349. Methods for transforming Acremonium chrysogenum are disclosed by Sumino et al., U.S. Patent No. 5,162,228. Methods for transforming Neurospora are disclosed by Lambowitz, U.S. Patent No. 4,486,533. Production of recombinant proteins in Pichia methanolica is disclosed in U.S. Patents No. 5,716,808, 5,736,383, 5,854,039, and 5,888,768; and WIPO publications WO 99/14347 and WO 99/14320.

Other higher eukaryotic cells, including plant cells and avian cells, can also be used as hosts according to methods commonly known in the art. For example, the use of *Agrobacterium rhizogenes* as a vector for expressing genes in plant cells has been reviewed by Sinkar et al., *J. Biosci.* (Bangalore) 11:47-58, 1987.

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Prokaryotic host cells, including strains of the bacteria *Escherichia coli*, *Bacillus* and other genera are also useful host cells within the present invention. Techniques for transforming these hosts and expressing foreign DNA sequences cloned therein are well known in the art (see, e.g., Sambrook et al., ibid.). When expressing a polypeptide in bacteria such as *E. coli*, the polypeptide may be retained in the

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cytoplasm, typically as insoluble granules, or may be directed to the periplasmic space by a bacterial secretion sequence. In the former case, the cells are lysed, and the granules are recovered and denatured using, for example, guanidine isothiocyanate or urea. The denatured polypeptide can then be refolded and dimerized by diluting the denaturant, such as by dialysis against a solution of urea and a combination of reduced and oxidized glutathione, followed by dialysis against a buffered saline solution. In the latter case, the polypeptide can be recovered from the periplasmic space in a soluble and functional form by disrupting the cells (by, for example, sonication or osmotic shock) to release the contents of the periplasmic space and recovering the protein, thereby obviating the need for denaturation and refolding.

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Transformed or transfected host cells are cultured according to conventional procedures in a culture medium containing nutrients and other components required for the growth of the chosen host cells. A variety of suitable media, including defined media and complex media, are known in the art and generally include a carbon source, a nitrogen source, essential amino acids, vitamins and minerals. Media may also contain such components as growth factors or serum, as required. The growth medium will generally select for cells containing the exogenously added DNA by, for example, drug selection or deficiency in an essential nutrient which is complemented by the selectable marker carried on the expression vector or co-transfected into the host cell.

It is preferred to purify the polypeptides and proteins of the present invention to ≥80% purity, more preferably to ≥90% purity, even more preferably ≥95% purity, and particularly preferred is a pharmaceutically pure state, that is greater than 99.9% pure with respect to contaminating macromolecules, particularly other proteins and nucleic acids, and free of infectious and pyrogenic agents. Preferably, a purified polypeptide or protein is substantially free of other polypeptides or proteins, particularly those of animal origin.

Expressed recombinant proteins (including single polypeptide chains, chimeric polypeptides, and polypeptide multimers) are purified by conventional protein purification methods, typically by a combination of chromatographic techniques. See, in general, Affinity Chromatography: Principles & Methods, Pharmacia LKB Biotechnology, Uppsala, Sweden, 1988; and Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York, 1994. Proteins comprising a polyhistidine affinity tag (typically about 6 histidine residues) are purified by affinity chromatography on a nickel chelate resin. See, for example, Houchuli et al., Bio/Technol. 6: 1321-1325, 1988. Proteins comprising a glu-glu tag can be purified by immunoaffinity chromatography essentially as disclosed by Grussenmeyer et al., ibid.

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Proteins comprising other affinity tags can be purified by appropriate affinity chromatography methods, which are known in the art.

Proteins of the present invention and fragments thereof can also be prepared through chemical synthesis according to methods known in the art, including exclusive solid phase synthesis, partial solid phase methods, fragment condensation or classical solution synthesis. See, for example, Merrifield, *J. Am. Chem. Soc.* 85:2149, 1963; Stewart et al., Solid Phase Peptide Synthesis (2nd edition), Pierce Chemical Co., Rockford, IL, 1984; Bayer and Rapp, Chem. Pept. Prot. 3:3, 1986; and Atherton et al., Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford, 1989.

Using methods known in the art, the proteins of the present invention can be prepared in a variety of modified or derivatized forms. For example, the proteins can be prepared glycosylated or non-glycosylated; pegylated or non-pegylated; and may or may not include an initial methionine amino acid residue.

Biological activities of the proteins of the present invention can be measured in vitro using cultured cells or in vivo by administering molecules of the claimed invention to the appropriate animal model. Many such assays and models are known in the art. Guidance in initial assay selection is provided by structural predictions and sequence alignments. However, even if no functional prediction is made, the activity of a protein can be elucidated by known methods, including, for example, screening a variety of target cells for a biological response, other in vitro assays, expression in a host animal, or through the use of transgenic and/or "knockout" animals. Through the application of robotics, many in vitro assays can be adapted to rapid, high-throughput screeing of a large number of samples. Target cells for use in activity assays include, without limitation, vascular cells (especially endothelial cells and smooth muscle cells), hematopoietic (myeloid and lymphoid) cells, liver cells (including hepatocytes, fenestrated endothelial cells, Kupffer cells, and Ito cells), fibroblasts (including human dermal fibroblasts and lung fibroblasts), neurite cells (including astrocytes, glial cells, dendritic cells, and PC-12 cells), fetal lung cells, articular synoviocytes, pericytes, chondrocytes, osteoblasts, adipocytes, and prostate epithelial cells. Endothelial cells and hematopoietic cells are derived from a common ancestral cell, the hemangioblast (Choi et al., Development 125:725-732, 1998).

Biological activity can be measured with a silicon-based biosensor microphysiometer that measures the extracellular acidification rate or proton excretion associated with receptor binding and subsequent physiologic cellular responses. An exemplary such device is the CytosensorTM Microphysiometer manufactured by Molecular Devices, Sunnyvale, CA. A variety of cellular responses, such as cell proliferation, ion transport, energy production, inflammatory response, regulatory and

receptor activation, and the like, can be measured by this method. See, for example, McConnell et al., Science 257:1906-1912, 1992; Pitchford et al., Meth. Enzymol. 228:84-108, 1997; Arimilli et al., J. Immunol. Meth. 212:49-59, 1998; and Van Liefde et al., Eur. J. Pharmacol. 346:87-95, 1998. The microphysiometer can be used for assaying adherent or non-adherent eukaryotic or prokaryotic cells. By measuring extracellular acidification changes in cell media over time, the microphysiometer directly measures cellular responses to various stimuli, including agonistic and antagonistic stimuli. Preferably, the microphysiometer is used to measure responses of a eukaryotic cell known to be responsive to the protein of interest, compared to a control eukaryotic cell that does not respond to the protein of interest. Responsive eukaryotic cells comprise cells into which a receptor for the protein of interest has been transfected, as well as naturally responsive cells. Differences in the response of cells exposed to the protein of interest, relative to a control not so exposed, are a direct measurement of protein-modulated cellular responses. Such responses can be assayed under a variety of stimuli. The present invention thus provides methods of identifying agonists and antagonists of proteins of interest, comprising providing cells responsive to a selected protein, culturing a first portion of the cells in the absence of a test compound, culturing a second portion of the cells in the presence of a test compound, and detecting a change in a cellular response of the second portion of the cells as 20 compared to the first portion of the cells. The change in cellular response is shown as a measurable change in extracellular acidification rate. Culturing a third portion of the cells in the presence of the protein of interest and the absence of a test compound provides a positive control and a control to compare the agonist activity of a test compound with that of the protein of interest. Antagonists can be identified by 25 exposing the cells to the protein of interest in the presence and absence of the test compound, whereby a reduction in protein-stimulated activity is indicative of antagonist activity in the test compound.

Assays measuring cell proliferation or differentiation are well known in the art. For example, assays measuring proliferation include such assays as chemosensitivity to neutral red dye (Cavanaugh et al., *Investigational New Drugs* 8:347-354, 1990), incorporation of radiolabelled nucleotides (as disclosed by, e.g., Raines and Ross, *Methods Enzymol.* 109:749-773, 1985; Wahl et al., *Mol. Cell Biol.* 8:5016-5025, 1988; and Cook et al., *Analytical Biochem.* 179:1-7, 1989), incorporation of 5-bromo-2'-deoxyuridine (BrdU) in the DNA of proliferating cells (Porstmann et al., *J. Immunol. Methods* 82:169-179, 1985), and use of tetrazolium salts (Mosmann, *J. Immunol. Methods* 65:55-63, 1983; Alley et al., *Cancer Res.* 48:589-601, 1988; Marshall et al., *Growth Reg.* 5:69-84, 1995; and Scudiero et al., *Cancer Res.* 48:4827-

4833, 1988). Differentiation can be assayed using suitable precursor cells that can be induced to differentiate into a more mature phenotype. Assays measuring differentiation include, for example, measuring cell-surface markers associated with stage-specific expression of a tissue, enzymatic activity, functional activity or morphological changes (Watt, FASEB, 5:281-284, 1991; Francis, Differentiation 57:63-75, 1994; Raes, Adv. Anim. Cell Biol. Technol. Bioprocesses, 161-171, 1989). Effects of a protein on tumor cell growth and metastasis can be analyzed using the Lewis lung carcinoma model, for example as described by Cao et al., J. Exp. Med. 182:2069-2077, 1995. Activity of a protein on cells of neural origin can be analyzed using assays that measure effects on neurite growth as disclosed below.

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In vitro assays for pro- and anti-inflammatory activity are known in the art. Exemplary activity assays include mitogenesis assays in which IL-1 responsive cells (e.g., D10.N4.M cells) are incubated in the presence of IL-1 or a test protein for 72 hours at 37°C in a 5% CO₂ atmosphere. IL-2 (and optionally IL-4) is added to the culture medium to enhance sensitivity and specificity of the assay. ³H-thymidine is then added, and incubation is continued for six hours. The amount of label incorporated is indicative of agonist activity. See, Hopkins and Humphreys, J. Immunol. Methods 120:271-276, 1989; Greenfeder et al., J. Biol. Chem. 270:22460-22466, 1995. Stimulation of cell proliferation can also be measured using thymocytes cultured in a test protein in combination with phytohemagglutinin. IL-1 is used as a control. Proliferation is detected as ³H-thymidine incorporation or metabolic breakdown of (MTT) (Mosman, ibid.).

Protein activity may also be detected using assays designed to measure induction of one or more growth factors or other macromolecules. Preferred such assays include those for determining the presence of hepatocyte growth factor (HGF), epidermal growth factor (EGF), transforming growth factor alpha (TGFα), interleukin-6 (IL-6), VEGF, acidic fibroblast growth factor (aFGF), angiogenin, and other macromolecules produced by the liver. Suitable assays include mitogenesis assays using target cells responsive to the macromolecule of interest, receptor-binding assays, competition binding assays, immunological assays (e.g., ELISA), and other formats known in the art. Metalloprotease secretion is measured from treated primary human dermal fibroblasts, synoviocytes and chondrocytes. The relative levels of collagenase, gelatinase and stromalysin produced in response to culturing a target cell in the presence of a protein of interest is measured using zymogram gels (Loita and Stetler-Stevenson, *Cancer Biology* 1:96-106, 1990). Procollagen/collagen synthesis by dermal fibroblasts and chondrocytes in response to a test protein is measured using ³H-proline incorporation into nascent secreted collagen.

SDS-PAGE followed by autoradiography (Unemori and Amento, *J. Biol. Chem.* 265: 10681-10685, 1990). Glycosaminoglycan (GAG) secretion from dermal fibroblasts and chondrocytes is measured using a 1,9-dimethylmethylene blue dye binding assay (Farndale et al., *Biochim. Biophys. Acta* 883:173-177, 1986). Collagen and GAG assays are also carried out in the presence of IL-1β or TGF-β to examine the ability of a protein to modify the established responses to these cytokines.

Monocyte activation assays are carried out (1) to look for the ability of a protein of interest to further stimulate monocyte activation, and (2) to examine the ability of a protein of interest to modulate attachment-induced or endotoxin-induced monocyte activation (Fuhlbrigge et al., *J. Immunol.* 138: 3799-3802, 1987). IL-1β and TNFα levels produced in response to activation are measured by ELISA (Biosource, Inc. Camarillo, CA). Monocyte/macrophage cells, by virtue of CD14 (LPS receptor), are exquisitely sensitive to endotoxin, and proteins with moderate levels of endotoxin-like activity will activate these cells.

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Other metabolic effects of proteins can be measured by culturing target cells in the presence and absence of a protein and observing changes in adipogenesis, gluconeogenesis, glycogenolysis, lipogenesis, glucose uptake, or the like. Suitable assays are known in the art.

Hematopoietic activity of proteins can be assayed on various hematopoietic cells in culture. Preferred assays include primary bone marrow colony assays and later stage lineage-restricted colony assays, which are known in the art (e.g., Holly et al., WIPO Publication WO 95/21920). Marrow cells plated on a suitable semi-solid medium (e.g., 50% methylcellulose containing 15% fetal bovine serum, 10% bovine serum albumin, and 0.6% PSN antibiotic mix) are incubated in the presence of test polypeptide, then examined microscopically for colony formation. Known hematopoietic factors are used as controls. Mitogenic activity of a protein of interest on hematopoietic cell lines can be measured as disclosed above.

Cell migration is assayed essentially as disclosed by Kähler et al. (Arteriosclerosis, Thrombosis, and Vascular Biology 17:932-939, 1997). A protein is considered to be chemotactic if it induces migration of cells from an area of low protein concentration to an area of high protein concentration. A typical assay is performed using modified Boyden chambers with a polystryrene membrane separating the two chambers (Transwell; Corning Costar Corp.). The test sample, diluted in medium containing 1% BSA, is added to the lower chamber of a 24-well plate containing Transwells. Cells are then placed on the Transwell insert that has been pretreated with 0.2% gelatin. Cell migration is measured after 4 hours of incubation at 37°C. Non-migrating cells are wiped off the top of the Transwell membrane, and cells

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attached to the lower face of the membrane are fixed and stained with 0.1% crystal violet. Stained cells are then extracted with 10% acetic acid and absorbance is measured at 600 nm. Migration is then calculated from a standard calibration curve. Cell migration can also be measured using the matrigel method of Grant et al. ("Angiogenesis as a component of epithelial-mesenchymal interactions" in Goldberg and Rosen, Epithelial-Mesenchymal Interaction in Cancer, Birkhäuser Verlag, 1995, 235-248; Baatout, Anticancer Research 17:451-456, 1997).

Proteins can be assayed for the ability to modulate axon guidance and growth. Suitable assays that detect changes in neuron growth patterns include, for example, those disclosed in Hastings, WIPO Publication WO 97/29189 and Walter et al., Development 101:685-96, 1987. Assays to measure the effects on neuron growth are well known in the art. For example, the C assay (e.g., Raper and Kapfhammer, Neuron 4:21-9, 1990 and Luo et al., Cell 75:217-27, 1993) can be used to determine collapsing activity of a protein of interest on growing neurons. Other methods that can assess protein-induced inhibition of neurite extension or divert such extension are also known. See, Goodman, Annu. Rev. Neurosci. 19:341-77, 1996. Conditioned media from cells expressing a protein of interest, or aggregates of such cells, can by placed in a gel matrix near suitable neural cells, such as dorsal root ganglia (DRG) or sympathetic ganglia explants, which have been co-cultured with nerve growth factor. Compared to control cells, protein-induced changes in neuron growth can be measured (as disclosed by, for example, Messersmith et al., Neuron 14:949-59, 1995 and Puschel et al., Neuron 14:941-8, 1995). Neurite outgrowth can be measured using neuronal cell suspensions grown in the presence of molecules of the present invention. See, for example, O'Shea et al., Neuron 7:231-7, 1991 and DeFreitas et al., Neuron 15:333-43, 1995.

Cell adhesion activity is assayed essentially as disclosed by LaFleur et al. (J. Biol. Chem. 272:32798-32803, 1997). Briefly, microtiter plates are coated with the test protein, non-specific sites are blocked with BSA, and cells (such as smooth muscle cells, leukocytes, or endothelial cells) are plated at a density of approximately 10⁴ - 10⁵ cells/well. The wells are incubated at 37°C (typically for about 60 minutes), then non-adherent cells are removed by gentle washing. Adhered cells are quantitated by conventional methods (e.g., by staining with crystal violet, lysing the cells, and determining the optical density of the lysate). Control wells are coated with a known adhesive protein, such as fibronectin or vitronectin.

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Assays for angiogenic activity are also known in the art. For example, the effect of a protein of interest on primordial endothelial cells in angiogenesis can be assayed in the chick chorioallantoic membrane angiogenesis assay (Leung, Science

246:1306-1309, 1989; Ferrara, Ann. NY Acad. Sci. 752:246-256, 1995). Briefly, a small window is cut into the shell of an eight-day old fertilized egg, and a test substance is applied to the chorioallantoic membrane. After 72 hours, the membrane is examined for neovascularization. Other suitable assays include microinjection of early stage quail (Coturnix coturnix japonica) embryos as disclosed by Drake et al. (Proc. Natl. Acad. Sci. USA 92:7657-7661, 1995); the rodent model of corneal neovascularization disclosed by Muthukkaruppan and Auerbach (Science 205:1416-1418, 1979), wherein a test substance is inserted into a pocket in the cornea of an inbred mouse; and the hampster cheek pouch assay (Höckel et al., Arch. Surg. 128:423-429, 1993). Induction of vascular permeability, which is indicative of angiogenic activity, is measured in assays designed to detect leakage of protein from the vasculature of a test animal (e.g., mouse or guinea pig) after administration of a test compound (Miles and Miles, J. Physiol. 118:228-257, 1952; Feng et al., J. Exp. Med. 183:1981-1986, 1996). In vitro assays for angiogenic activity include the tridimensional collagen gel matrix model (Pepper et al. Biochem. Biophys. Res. Comm. 189:824-831, 1992 and Ferrara et al., Ann. NY Acad. Sci. 732:246-256, 1995), which measures the formation of tube-like structures by microvascular endothelial cells; and matrigel models (Grant et al., "Angiogenesis as a component of epithelialmesenchymal interactions" in Goldberg and Rosen, Epithelial-Mesenchymal Interaction in Cancer, Birkhäuser Verlag, 1995, 235-248; Baatout, Anticancer Research 17:451-456, 1997), which are used to determine effects on cell migration and tube formation by endothelial cells seeded in matrigel, a basement membrane extract enriched in laminin. It is preferred to carry out angiogenesis assays in the presence and absence of vascular endothelial growth factor (VEGF) to assess possible combinatorial effects. It is also preferred to use VEGF as a control within in vivo assays.

Receptor binding can be measured by the competition binding method of Labriola-Tompkins et al., *Proc. Natl. Acad. Sci. USA* 88:11182-11186, 1991. In an exemplary assay for IL-1 receptor binding, membranes pepared from EL-4 thymoma cells (Paganelli et al., *J. Immunol.* 138:2249-2253, 1987) are incubated in the presence of the test protein for 30 minutes at 37°C. Labeled IL-1 α or IL-1 β is then added and the incubation is continued for 60 minutes. The assay is terminated by membrane filtration. The amount of bound label is determined by conventional means (e.g., γ counter). In an alternative assay, the ability of a test protein to compete with labeled IL-1 for binding to cultured human dermal fibroblasts is measured according to the method of Dower et al. (*Nature* 324:266-268, 1986). Briefly, cells are incubated in a round-bottomed, 96-well plate in a suitable culture medium (e.g., RPMI 1640 containing 1% BSA, 0.1% Na azide, and 20 mM HEPES pH 7.4) at 8°C on a rocker

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platform in the presence of labeled IL-1. Various concentrations of test protein are added. After the incubation (typically about two hours), cells are separated from unbound label by centrifuging 60-µl aliquots through 200 µl of phthalate oils in 400-µl polyethylene centrifuge tubes and excising the tips of the tubes with a razor blade as disclosed by Segal and Hurwitz, *J. Immunol.* 118:1338-1347, 1977. Receptor binding assays for other cell types are known in the art. See, for example, Bowen-Pope and Ross, *Methods Enzymol.* 109:69-100, 1985.

Receptor binding can also be measured using immobilized receptors or ligand-binding receptor fragments. For example, an immobilized receptor can be exposed to its labeled ligand and unlabeled test protein, whereby a reduction in labeled ligand binding compared to a control is indicative of receptor-binding activity in the test protein. Within another format, a receptor or ligand-binding receptor fragment is immobilized on a biosensor (e.g., BIACoreTM, Pharmacia Biosensor, Piscataway, NJ) and binding is determined. Antagonists of the native ligand will exhibit receptor binding but will exhibit essentially no activity in appropriate activity assays or will reduce the ligand-mediated response when combined with the native ligand. In view of the low level of receptor occupancy required to produce a response to some ligands (e.g., IL-1), a large excess of antagonist (typically a 10- to 1000-fold molar excess) may be necessary to neutralize ligand activity.

Receptor activation can be detected in target cells by: (1) measurement of adenylate cyclase activity (Salomon et al., Anal. Biochem. 58:541-48, 1974; Alvarez and Daniels, Anal. Biochem. 187:98-103, 1990); (2) measurement of change in intracellular cAMP levels using conventional radioimmunoassay methods (Steiner et al., J. Biol. Chem. 247:1106-13, 1972; Harper and Brooker, J. Cyc. Nucl. Res. 1:207-18, 1975); or (3) through use of a cAMP scintillation proximity assay (SPA) method (such as available from Amersham Corp., Arlington Heights, IL).

Proteins can be tested for serine protease activity or proteinase inhibitory activity using conventional assays. Substrate cleavage is conveniently assayed using a tetrapeptide that mimics the cleavage site of the natural substrate and which is linked, via a peptide bond, to a carboxyl-terminal para-nitro-anilide (pNA) group. The protease hydrolyzes the bond between the fourth amino acid residue and the pNA group, causing the pNA group to undergo a dramatic increase in absorbance at 405 nm. Suitable substrates can be synthesized according to known methods or obtained from commercial suppliers. Inhibitory activity is measured by adding a test sample to a reaction mixture containing enzyme and substrate, and comparing the observed enzyme activity to a control (without the test sample). A variety of such assays are known in the art, including assays measuring inhibition of trypsin,

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chymotrypsin, plasmin, cathepsin G, and human leukocyte elastase. See, for example, Petersen et al., Eur. J. Biochem. 235:310-316, 1996. In a typical procedure, the inhibitory activity of a test compound is measured by incubating the test compound with the proteinase, then adding an appropriate substrate, typically a chromogenic peptide substrate. See, for example, Norris et al. (Biol. Chem. Hoppe-Seyler 371:37-42, 1990). Various concentrations of the inhibitor are incubated in the presence of trypsin, plasmin, and plasma kallikrein in a low-salt buffer at pH 7.4, 25°C. After 30 minutes, the residual enzymatic activity is measured by the addition of a chromogenic substrate (e.g., S2251 (D-Val-Leu-Lys-Nan) or S2302 (D-Pro-Phe-Arg-Nan), available from Kabi, Stockholm, Sweden) and a 30-minute incubation. Inhibition of enzyme activity is indicated by a decrease in absorbance at 405 nm or fluorescence Em at 460 nm. From the results, the apparent inhibition constant K_i is calculated. When a serine protease is prepared as an active precursor (e.g., comprising N-terminal residues 1-109 of SEQ ID NO:2), it is activated by cleavage with a suitable protease (e.g., furin (Steiner et al., J. Biol. Chem. 267:23435-23438, 1992)) prior to assay. Assays of this type are well known in the art. See, for example, Lottenberg et al., Thrombosis Research 28:313-332, 1982; Cho et al., Biochem. 23:644-650, 1984; Foster et al., Biochem. 26:7003-7011, 1987). The inhibition of coagulation factors (e.g., factor VIIa, factor Xa) can be measured using chromogenic substrates or in conventional coagulation assays (e.g., clotting time of normal human plasma; Dennis et al., J. Biol. Chem. 270:25411-25417, 1995).

Blood coagulation and chromogenic assays, which can be used to detect both procoagulant, anticoagulant, and thrombolytic activities, are known in the art. For example, pro- and anticoagulant activities can be measured in a one-stage clotting assay using platelet-poor or factor-deficient plasma (Levy and Edgington, *J. Exp. Med.* 151:1232-1243, 1980; Schwartz et al., *J. Clin. Invest.* 67:1650-1658, 1981). As disclosed by Anderson et al. (*Proc. Natl. Acad. Sci. USA* 96:11189-11193, 1999), the effect of a test compound on platelet activation can be determined by a change in turbidity, and the procoagulant activity of activated platelets can be determined in a phospholipid-dependent coagulation assay. Activation of thrombin can be determined by hydrolysis of peptide p-nitroanilide substrates as disclosed by Lottenberg et al. (*Thrombosis Res.* 28:313-332, 1982). Other procoagulant, anticoagulant, and thrombolytic activities can be measured using appropriate chromogenic substrates, a variety of which are available from commercial suppliers. See, for example, Kettner and Shaw, *Methods Enzymol.* 80:826-842, 1981.

Anti-microbial activity of proteins is evaluated by techniques that are known in the art. For example, anti-microbial activity can be assayed by evaluating the

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sensitivity of microbial cell cultures to test agents and by evaluating the protective effect of test agents on infected mice. See, for example, Musiek et al., Antimicrob. Agents Chemothr. 3:40, 1973. Antiviral activity can also be assessed by protection of mammalian cell cultures. Known techniques for evaluating anti-microbial activity include, for example, Barsum et al., Eur. Respir. J. 8:709-714, 1995; Sandovsky-Losica et al., J. Med. Vet. Mycol (England) 28:279-287, 1990; Mehentee et al., J. Gen. Microbiol (England) 135(:2181-2188, 1989; and Segal and Savage, J. Med. Vet. Mycol. 24:477-479, 1986. Assays specific for anti-viral activity include, for example, those described by Daher et al., J. Virol. 60:1068-1074, 1986.

The assays disclosed above can be modified by those skilled in the art to detect the presence of agonists and antagonists of a selected protein of interest.

Expression of a polynucleotide encoding a protein of interest in animals provides models for further study of the biological effects of overproduction or inhibition of protein activity *in vivo*. Polynucleotides and antisense polynucleotides can be introduced into test animals, such as mice, using viral vectors or naked DNA, or transgenic animals can be produced.

One *in vivo* approach for assaying proteins of the present invention utilizes viral delivery systems. Exemplary viruses for this purpose include adenovirus, herpesvirus, retroviruses, vaccinia virus, and adeno-associated virus (AAV). Adenovirus, a double-stranded DNA virus, is currently the best studied gene transfer vector for delivery of heterologous nucleic acids. For review, see Becker et al., *Meth. Cell Biol.* 43:161-89, 1994; and Douglas and Curiel, *Science & Medicine* 4:44-53, 1997. The adenovirus system offers several advantages. Adenovirus can (i) accommodate relatively large DNA inserts; (ii) be grown to high-titer; (iii) infect a broad range of mammalian cell types; and (iv) be used with many different promoters including ubiquitous, tissue specific, and regulatable promoters. Because adenoviruses are stable in the bloodstream, they can be administered by intravenous injection.

By deleting portions of the adenovirus genome, larger inserts (up to 7 kb) of heterologous DNA can be accommodated. These inserts can be incorporated into the viral DNA by direct ligation or by homologous recombination with a cotransfected plasmid. In an exemplary system, the essential E1 gene is deleted from the viral vector, and the virus will not replicate unless the E1 gene is provided by the host cell (e.g., the human 293 cell line). When intravenously administered to intact animals, adenovirus primarily targets the liver. If the adenoviral delivery system has an E1 gene deletion, the virus cannot replicate in the host cells. However, the host's tissue (e.g., liver) will express and process (and, if a signal sequence is present, secrete) the

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heterologous protein. Secreted proteins will enter the circulation in the highly vascularized liver, and effects on the infected animal can be determined.

An alternative method of gene delivery comprises removing cells from the body and introducing a vector into the cells as a naked DNA plasmid. The transformed cells are then re-implanted in the body. Naked DNA vectors are introduced into host cells by methods known in the art, including transfection, electroporation, microinjection, transduction, cell fusion, DEAE dextran, calcium phosphate precipitation, use of a gene gun, or use of a DNA vector transporter. See, Wu et al., *J. Biol. Chem.* 263:14621-14624, 1988; Wu et al., *J. Biol. Chem.* 267:963-967, 1992; and Johnston and Tang, *Meth. Cell Biol.* 43:353-365, 1994.

Transgenic mice, engineered to express a gene encoding a protein of interest, and mice that exhibit a complete absence of gene function, referred to as "knockout mice" (Snouwaert et al., Science 257:1083, 1992), can also be generated (Lowell et al., Nature 366:740-742, 1993). These mice can be employed to study the gene of interest and the protein encoded thereby in an in vivo system. Transgenic mice are particularly useful for investigating the role of proteins in early development in that they allow the identification of developmental abnormalities or blocks resulting from the over- or underexpression of a specific factor. See also, Maisonpierre et al., Science 277:55-60, 1997 and Hanahan, Science 277:48-50, 1997. Preferred promoters for transgenic expression include promoters from metallothionein and albumin genes. As disclosed above, the human sequences provided herein can be used to clone orthologous polynucleotides, which may be preferred for use in generating transgenic and knockout animals.

Antisense methodology can be used to inhibit gene transcription to examine the effects of such inhibition in vivo. Polynucleotides that are complementary to a segment of a protein-encoding polynucleotide are designed to bind to the encoding mRNA and to inhibit translation of such mRNA. Such antisense oligonucleotides can also be used to inhibit expression of protein-encoding genes in cell culture.

Biological activities of test proteins can also be measured in animal models by administering the test protein, by itself or in combination with other agents, including other proteins. Using such models facilitates the assay of the test protein by itself or as an inhibitor or modulator of another agent, and also facilitates the measurement of combinatorial effects of bioactive compounds.

Anti-inflammatory activity can be tested in animal models of inflammatory disease. For example, animal models of psoriasis include the analysis of histological alterations in adult mouse tail epidermis (Hofbauer et al, *Brit. J. Dermatol.*

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118:85-89, 1988; Bladon et al., Arch Dermatol. Res. 277:121-125, 1985). In this model, anti-psoriatic activity is indicated by the induction of a granular layer and orthokeratosis in areas of scale between the hinges of the tail epidermis. Typically, a topical ointment comprising a test compound is applied daily for seven consecutive days, then the animal is sacrificed, and tail skin is examined histologically. An additional model is provided by grafting psoriatic human skin to congenitally athymic (nude) mice (Krueger et al., J. Invest. Dermatol. 64:307-312, 1975). Such grafts have been shown to retain the characteristic histology for up to eleven weeks. As in the mouse tail model, the test composition is applied to the skin at predetermined intervals for a period of one to several weeks, at which time the animals are sacrificed and the skin grafts examined histologically. A third model has been disclosed by Fretland et al. (Inflammation 14:727-739, 1990). Briefly, inflammation is induced in guinea pig epidermis by topically applying phorbol ester (phorbol-12-myristate-13-acetate; PMA), typically at ca. 2 g/ml in acetone, to one ear and vehicle to the contralateral ear. Test compounds are applied concurrently with the PMA, or may be given orally. Histological analysis is performed at 96 hours after application of PMA. This model duplicates many symptoms of human psoriasis, including edema, inflammatory cell diapedesis and infiltration, high LTB4 levels and epidermal proliferation.

Cerebral ischemia can be studied in a rat model as disclosed by Relton et al. (*ibid.*) and Loddick et al. (*ibid.*).

The effect of a test protein on primordial endothelial cells in angiogenesis can be assayed in the chick chorioallantoic membrane angiogenesis assay (Leung, Science 246:1306-1309, 1989; Ferrara, Ann. NY Acad. Sci. 752:246-256, 1995). Briefly, a small window is cut into the shell of an eight-day old fertilized egg, and a test substance is applied to the chorioallantoic membrane. After 72 hours, the membrane is examined for neovascularization. Embryo microinjection of early stage quail (Coturnix coturnix japonica) embryos can also be used (Drake et al., Proc. Natl. Acad. Sci. USA 92:7657-7661, 1995). Briefly, a solution containing the protein is injected into the interstitial space between the endoderm and the splanchnic mesoderm of early-stage embryos using a micropipette and micromanipulator system. After injection, embryos are placed ventral side down on a nutrient agar medium and incubated for 7 hours at 37°C in a humidified CO₂/air mixture (10%/90%). Vascular development is assessed by microscopy of fixed, whole-mounted embryos and sections.

35 Stimulation of coronary collateral growth can be measured in known animal models, including a rabbit model of peripheral limb ischemia and hind limb ischemia and a pig model of chronic myocardial ischemia (Ferrara et al., *Endocrine*

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Reviews 18:4-25, 1997). Test proteins are assayed in the presence and absence of VEGF and basic FGF to test for combinatorial effects. These models can be modified by the use of adenovirus or naked DNA for gene delivery as disclosed in more detail above, resulting in local expression of the test protein(s).

Angiogenic activity can also be tested in a rodent model of corneal neovascularization as disclosed by Muthukkaruppan and Auerbach, *Science* 205:1416-1418, 1979, wherein a test substance is inserted into a pocket in the cornea of an inbred mouse. For use in this assay, proteins are combined with a solid or semi-solid, biocompatible carrier, such as a polymer pellet. Angiogenesis is followed microscopically. Vascular growth into the corneal stroma can be detected in about 10 days.

Angiogenic activity can also be tested in the hampster cheek pouch assay (Höckel et al., Arch. Surg. 128:423-429, 1993). A test substance is injected subcutaneiously into the cheek pouch, and after five days the pouch is examined under low magnification to determine the extent of neovascularization. Tissue sections can also be examined histologically.

Induction of vascular permeability is measured in assays designed to detect leakage of protein from the vasculature of a test animal (e.g., mouse or guinea pig) after administration of a test compound (Miles and Miles, *J. Physiol.* 118:228-257, 1952; Feng et al., *J. Exp. Med.* 183:1981-1986, 1996).

Wound-healing models include the linear skin incision model of Mustoe et al. (Science 237:1333, 1987). In a typical procedure, a 6-cm incision is made in the dorsal pelt of an adult rat, then closed with wound clips. Test substances and controls (in solution, gel, or powder form) are applied before primary closure. It is preferred to limit administration to a single application, although additional applications can be made on succeeding days by careful injection at several sites under the incision. Wound breaking strength is evaluated between 3 and 21 days post wounding. In a second model, multiple, small, full-thickness excisions are made on the ear of a rabbit. The cartilage in the ear splints the wound, removing the variable of wound contraction from the evaluation of closure. Experimental treatments and controls are applied. The geometry and anatomy of the wound site allow for reliable quantification of cell ingrowth and epithelial migration, as well as quantitative analysis of the biochemistry of the wounds (e.g., collagen content). See, Mustoe et al., J. Clin. Invest. 87:694, 1991. The rabbit ear model can be modified to create an ischemic wound environment, which more closely resembles the clinical situation (Ahn et al., Ann. Plast. Surg. 24:17, 1990). Within a third model, healing of partial-thickness skin wounds in pigs or guinea pigs is evaluated (LeGrand et al., Growth Factors 8:307, 1993). Experimental

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treatments are applied daily on or under dressings. Seven days after wounding, granulation tissue thickness is determined. This model is preferred for dose-response studies, as it is more quantitative than other in vivo models of wound healing. A full thickness excision model can also be employed. Within this model, the epidermis and dermis are removed down to the panniculus carnosum in rodents or the subcutaneous fat in pigs. Experimental treatments are applied topically on or under a dressing, and can be applied daily if desired. The wound closes by a combination of contraction and cell ingrowth and proliferation. Measurable endpoints include time to wound closure, histologic score, and biochemical parameters of wound tissue. Impaired wound healing models are also known in the art (e.g., Cromack et al., Surgery 113:36, 1993; Pierce et al., Proc. Natl. Acad. Sci. USA 86:2229, 1989; Greenhalgh et al., Amer. J. Pathol. 136:1235, 1990). Delay or prolongation of the wound healing process can be induced pharmacologically by treatment with steroids, irradiation of the wound site, or by concomitant disease states (e.g., diabetes). Linear incisions or full-thickness excisions are most commonly used as the experimental wound. Endpoints are as disclosed above for each type of wound. Subcutaneous implants can be used to assess compounds acting in the early stages of wound healing (Broadley et al., Lab. Invest. 61:571, 1985; Sprugel et al., Amer. J. Pathol. 129: 601, 1987). Implants are prepared in a porous, relatively non-inflammatory container (e.g., polyethylene sponges or expanded polytetrafluoroethylene implants filled with bovine collagen) and placed subcutaneously in mice or rats. The interior of the implant is empty of cells, producing a "wound space" that is well-defined and separable from the preexisting tissue. This arrangement allows the assessment of cell influx and cell type as well as the measurement of vasculogenesis/angiogenesis and extracellular matrix production.

Inhibition of tumor metastasis can be assessed in mice into which cancerous cells or tumor tissue have been introduced by implantation or injection (e.g., Brown, *Advan. Enzyme Regul.* 35:293-301, 1995; Conway et al., *Clin. Exp. Metastasis* 14:115-124, 1996).

Effects on fibrinolysis can be measured in a rat model wherein the enzyme batroxobin and radiolabeled fibrinogen are administered to test animals. Inhibition of fibrinogen activation by a test compound is seen as a reduction in the circulating level of the label as compared to animals not receiving the test compound. See, Lenfors and Gustafsson, Semin. Thromb. Hemost. 22:335-342, 1996.

The invention further provides polypeptides that comprise an epitopebearing portion of a protein as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 436. An "epitope" is a region of a protein to which an antibody can bind. See, for example, Geysen et al., *Proc. Natl. Acad. Sci. USA* 81:3998-4002, 1984. Epitopes can be linear or conformational, the latter being composed of discontinuous regions of the protein that form an epitope upon folding of the protein. Linear epitopes are generally at least 6 amino acid residues in length. Relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for example, Sutcliffe et al., Science 219:660-666, 1983. Antibodies that recognize short, linear epitopes are particularly useful in analytic and diagnostic applications that employ denatured protein, such as Western blotting (Tobin, Proc. Natl. Acad. Sci. USA 76:4350-4356, 1979). Antibodies to short peptides may also recognize proteins in native conformation and will thus be useful for monitoring protein expression and protein isolation, and in detecting proteins in solution, such as by ELISA or in immunoprecipitation studies.

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Antigenic, epitope-bearing polypeptides of the present invention are useful for raising antibodies, including monoclonal antibodies, that specifically bind to the corresponding protein. Antigenic, epitope-bearing polypeptides contain a sequence of at least six, preferably at least nine, more preferably from 15 to about 30 contiguous amino acid residues of a protein. Within certain embodiments of the invention, the polypeptides comprise 40, 50, 100, or more contiguous residues of a protein as shown in SEQ ID NO:M, up to the entire predicted mature protein or the primary translation product. It is preferred that the amino acid sequence of the epitope-bearing polypeptide is selected to provide substantial solubility in aqueous solvents, that is the sequence includes relatively hydrophilic residues, and hydrophobic residues are substantially avoided. Table 10 lists preferred hexapeptides for use as antigens. Within Table 10, each the amino termini of the hexapeptides are specified. Those skilled in the art will recognize that longer polypeptides comprising these hexapeptides can also be used and will often be preferred.

		<u>Tal</u>	<u>ble 10</u>		
Protein		Hexa	peptide N	<u>-termini</u>	
AFP210015	389	405	97	388	359
AFP170681	51	334	113	49	140
AFP413680	221	207	220	206	198
AFP483037	219	218	82	216	215
AFP230872	189	188	73	156	68
AFP178828	211	210	209	208	207
AFP200134	150	149	146	132	145
AFP195796	99	97	111	208	240
AFP483037 AFP230872 AFP178828 AFP200134	219 189 211 150	218 188 210 149	82 73 209 146	216 156 208 132	2 6 2 1

AFP477303	64	126	63	54	112
AFP354334	269	268	267	266	265
AFP250287	34	33	48	2	143
AFP177000	133	132	104	37	68
AFP278176	234	145	.284	91	291
AFP202885	134	244	170	133	243
AFP221312	31	29	28	51	43
AFP239757	329	200	556	107	328
AFP226311	293	74	250	86	184
AFP305901	340	194	451	192	120
AFP325549	293	74	250	86	184
AFP81988	151	167	147	165	173
AFP199200	150	149	148	92	147
AFP290395	31	29	28	329	326
AFP212675	67	66	65	204	396
AFP326051	49	56	23	78	95
AFP512441	94	93	41	39	38
AFP55098	140	34	139	120	32
AFP169796	177	173	156	32	155
AFP280706	33	54	32	31	53
AFP383165	25	82	52	24	178
AFP195467	113	112	71	2	80
AFP134225	114	280	113	455	417
AFP261193	120	66	65	85	119
AFP324422	147	145	66	65	85
AFP374312	125	124	79	123	77
AFP258118	64	63	116	115	62
AFP74517	1	72	124	123	22
AFP254653	134	36	62	14	23
AFP108666	79	76	74	49	48
AFP8766	140	34	139	120	298
AFP397185	265	35	264	34	48
AFP195042	192	535	191	259	533
AFP310695	49	75	190	5	94
AFP70022	38	64	179	83	37
AFP121670	184	183	121	118	182
AFP345861	151	89	75	135	149

AFP395942	60	14	59	13	21
AFP170291	144	72	56	55	63
AFP297548	145	73	57	56	64
AFP188135	152	148	158	147	144
AFP302388	478	431	416	414	429
AFP263430	92	23	64	91	110
AFP201273	373	384	163	372	44
AFP98983	3	2	35	34	32
AFP581958	71	66	80	26	25
AFP404202	1	31	115	30	92
AFP207203	427	258	204	426	48
AFP220790	139	92	51	187	91
AFP536326	87	146	105	73	103
AFP257473	270	205	203	245	244
AFP248380	283	62	54	272	100
AFP276202	50	48	35	46	33
AFP227568	199	23	238	363	224
AFP229039	226	91	116	161	225
AFP176297	261	382	183	119	182
AFP356885	622	45	525	175	466
AFP226938	118	108	117	79	107
AFP138504	77	255	75	254	292
AFP359196	4	76	3	2	37
AFP501809	141	139	9	169	2
AFP152733	258	204	48	47	257
AFP541394	31	29	28	235	232
AFP243183	272	110	106	3	2
AFP80739	398	397	224	223	155
AFP361806	4	78	139	3	76
AFP483930	107	124	123	88	45
AFP257336	124	42	122	182	158
AFP195800	40	39	65	38	96
AFP179530	57	251	249	315	55
AFP279267	106	62	216	187	59
AFP299766	127	168	165	29	126
AFP244615	171	196	326	255	179
AFP325761	138	137	2	144	109

AFP226024	79	317	159	140	45
AFP257094	71	116	115	3	144
AFP197103	200	198	215	195	177
AFP271855	92	44	42	18	27
AFP324816	9	252	120	8	63
AFP407963	202	201	156	200	155
AFP369635	98	398	255	97	254
AFP93743	4	254	3	294	293
AFP243230	28	129	128	127	44
AFP169316	294	170	293	36	157
AFP130852	82	59	117	145	66
AFP194191	363	. 112	271	69	267
AFP213472	103	102	69	2	37
AFP360430	177	75	183	74	130
AFP491309	107	106	69	2	37
AFP193428	129	87	343	60	128
AFP366534	72	4	2	59	39
AFP22706	229	227	65	64	188
AFP389012	216	27	289	34	17
AFP137186	2	1	182	216	43
AFP127023	. 86	56	131	178	55
AFP389687	57	56	117	370	369
AFP293220	186	194	105	146	182
AFP425535	264	181	163	370	149
AFP301494	159	4	2	84	25
AFP345421	500	592	639	652	849
AFP216667	92	435	329	422	47
AFP247951	27	34	33	25	94
AFP4464	365	363	362	55	209
AFP561930	108	107	104	52	66 .
AFP192851	300	276	299	298	496
AFP252759	311	310	64	21	157
AFP199044	143	2	209	206	125
AFP357958	167	338	165	324	362
AFP117501	135	87	362	86	418
AFP194554	318	170	54	105	169
AFP371069	332	1	283	365	279

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AFP313600	341	340	240	48	176
AFP262739	25	24	142	23	207
AFP180730	58	37	30	27	36
AFP287227	596	592	591	374	525
AFP75785	128	127	136	99	71
AFP174843	152	323	150	309	347
AFP250422	100	140	99	138	182
AFP198645	145	144	143	64	56
AFP238111	123	50	20	137	35
AFP460626	153	151	71	150	70
AFP271081	68	112	39	202	67
AFP277752	109	106	220	238	92
AFP291338	347	342	97	362	339
AFP551038	134	131	186	130	173
AFP301579	105	153	130	152	67
AFP266188	121	235	61	180	120
AFP275580	193	77	192	2	148
AFP298054	148	234	146	233	144
AFP348226	148	103	85	309	59
AFP349106	208	118	117	207	116
AFP288248	376	342	340	339	312
AFP436476	18	39	139	38	99
AFP352125	53	59	163	142	104
AFP62060	247	187	73	426	72
AFP236718	100	99	249	248	184
AFP75775	201	90	239	173	199
AFP407487	148	103	85	59	58
AFP280451	141	294	6	209	139
AFP11675	58	56	90	64	89
AFP348656	160	159	158	103	149
AFP277451	118	2	1	146	241
AFP287436	53	59	223	142	104
AFP116043	212	239	138	186	183
AFP138740	264	263	31	72	232
AFP15192	47	46	216	85	212
AFP169968	64	117	63	2	81
AFP173341	65	64	102	101	100

AFP17588	43	42	2	41	1
AFP176427	311	290	308	155	288
AFP192633	58	56	162	349	44
AFP193013	47	90	87	46	68
AFP193881	274	295	402	273	292
AFP195562	274	295	339	473	273
AFP199922	57	55	74	180	50
AFP204736	89	58	43	28	23
AFP206179	74	80	73	71	70
AFP221877	32	31	30	50	75
AFP222758	44	43	75	42	19
AFP227032	47	55	46	65	54
AFP229269	147	127	146	63	60
AFP232213	44	41	28	27	40
AFP237679	2	1	34	58	55
AFP249599	48	47	45	43	42
AFP275215	82	80	70	2	55
AFP290397	149	148	2	1	29
AFP306591	45	44	84	83	65
AFP310297	23	31	37	47	30
AFP314720	47	44	26	25	23
AFP318671	55	54	51	64	63
AFP323575	75	73	72	70	18
AFP327160	37	68	47	67	96
AFP329002	78	77	76	75	74
AFP345415	41	40	133	106	39
AFP347179	30	4	29	86	177
AFP359138	77 .	2	76	75	74
AFP365372	13	I	62	69	79
AFP367284	61	60	36	5	59
AFP372822	49	48	25	8	24
AFP374595	154	153	165	3	56
AFP375952	36	35	53	52	69
AFP382913	67	32	30	20	66
AFP389184	24	31	78	30	39
AFP404208	69	68	67	39	36
AFP404279	81	31	72	30	62

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AFP409112	97	96	56	94	55
AFP413111	65	85	96	64	94
AFP415635	35	26	25	34	32
AFP421092	27	1	46	57	35
AFP436666	5	95	59	4	58
AFP448623	14				
AFP454192	106	104	83	114	112
AFP49026	49	104	76	48	138
AFP51688	51	86	50	85	43
AFP525341	18	17	16	79	14
AFP545268	65	64	75	21	74
AFP592620	22	21	29	20	28
AFP62197	134	84	133	20	104
AFP68229	161	171	192	170	232
AFP71288	67	49	65	48	46
AFP77851	123	121	33	103	53
AFP81957	89	66	63	25	40
AFP85168	61	31	39	27	46

As used herein, the term "antibodies" includes polyclonal antibodies, monoclonal antibodies, antigen-binding fragments thereof such as F(ab')₂ and Fab fragments, single chain antibodies, and the like, including genetically engineered antibodies. Non-human antibodies can be humanized by grafting only non-human CDRs onto human framework and constant regions, or by incorporating the entire non-human variable domains (optionally "cloaking" them with a human-like surface by replacement of exposed residues, wherein the result is a "veneered" antibody). In some instances, humanized antibodies may retain non-human residues within the human variable region framework domains to enhance proper binding characteristics. Through humanizing antibodies, biological half-life may be increased, and the potential for adverse immune reactions upon administration to humans is reduced. One skilled in the art can generate humanized antibodies with specific and different constant domains (i.e., different Ig subclasses) to facilitate or inhibit various immune functions associated with particular antibody constant domains.

Alternative techniques for generating or selecting antibodies useful herein include *in vitro* exposure of lymphocytes to an immunogenic polypeptide, and selection of antibody display libraries in phage or similar vectors (for instance, through use of an immobilized or labeled polypeptide). Human antibodies can be produced in

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transgenic, non-human animals that have been engineered to contain human immunoglobulin genes as disclosed in WIPO Publication WO 98/24893. It is preferred that the endogenous immunoglobulin genes in these animals be inactivated or eliminated, such as by homologous recombination.

Antibodies are defined to be specifically binding if they bind to a target polypeptide with an affinity at least 10-fold greater than the binding affinity to control (non-target) polypeptide. It is preferred that the antibodies exhibit a binding affinity (K_a) of 10⁶ M⁻¹ or greater, preferably 10⁷ M⁻¹ or greater, more preferably 10⁸ M⁻¹ or greater, and most preferably 10⁹ M⁻¹ or greater. The affinity of a monoclonal antibody can be readily determined by one of ordinary skill in the art (see, for example, Scatchard, *Ann. NY Acad. Sci.* 51: 660-672, 1949).

Methods for preparing polyclonal and monoclonal antibodies are well known in the art (see for example, Hurrell, J. G. R., Ed., Monoclonal Hybridoma Antibodies: Techniques and Applications, CRC Press, Inc., Boca Raton, FL, 1982). As would be evident to one of ordinary skill in the art, polyclonal antibodies can be generated from a variety of warm-blooded animals such as horses, cows, goats, sheep, dogs, chickens, rabbits, mice, and rats. The immunogenicity of a polypeptide immunogen may be increased through the use of an adjuvant such as alum (aluminum hydroxide) or Freund's complete or incomplete adjuvant. Polypeptides useful for immunization also include fusion polypeptides, such as fusions of a polypeptide of interest or a portion thereof with an immunoglobulin polypeptide or with maltose binding protein. The polypeptide immunogen may be a full-length molecule or a portion thereof. If the polypeptide portion is "hapten-like", such portion may be advantageously joined or linked to a macromolecular carrier (such as keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA) or tetanus toxoid) for immunization.

A variety of assays known to those skilled in the art can be utilized to detect antibodies that specifically bind to a polypeptide of interest. Exemplary assays are described in detail in *Antibodies: A Laboratory Manual*, Harlow and Lane (Eds.), Cold Spring Harbor Laboratory Press, 1988. Representative examples of such assays include concurrent immunoelectrophoresis, radio-immunoassays, radio-immunoprecipitations, enzyme-linked immunosorbent assays (ELISA), dot blot assays, Western blot assays, inhibition or competition assays, and sandwich assays.

Antibodies can be used, for example, to isolate target polypeptides by affinity purification, for diagnostic assays for determining circulating or localized levels of target polypeptides, for tissue typing, for cell sorting, for screening expression libraries; for generating anti-idiotypic antibodies, and as neutralizing antibodies or as antagonists to block protein activity *in vitro* and *in vivo*.

The present invention also provides reagents for use in diagnostic and therapeutic applications. Such reagents include polynucleotide probes and primers; antibodies, including antibody fragments, single-chain antibodies, and other genetically engineered forms; soluble receptors and other polypeptide binding partners; and the proteins of the invention themselves, including fragments thereof. Those skilled in the art will recognize that diagnostic reagents will commonly be labeled to provide a detectable signal or other second function. Thus, polypeptides, antibodies, receptors, and other binding partners disclosed herein can be directly or indirectly conjugated to drugs, toxins, radionuclides, enzymes, enzyme substrates, cofactors, inhibitors, fluorescent markers, chemiluminescent markers, magnetic particles, and the like, and these conjugates used for in vivo diagnostic or therapeutic applications. Cytotoxic molecules, for example, can be directly or indirectly attached to the binding partner (e.g., by chemical coupling or as a fusion protein), and include bacterial or plant toxins (e.g., diphtheria toxin, *Pseudomonas* exotoxin, ricin, saporin, abrin, and the like); therapeutic radionuclides (e.g., iodine-131, rhenium-188 or yttrium-90) which can be directly attached to a polypeptide or antibody or indirectly attached through means of a chelating moiety; and cytotoxic drugs (e.g., adriamycin). Methods for preparing labeled reagents are known in the art. Within an alternative embodiment, the detectable signal or other function can be provided by a second member of a complement-anticomplement pair, which second member binds to the diagnostic reagent. For example, a first (unlabeled) antibody can be used to bind to a cell-surface polypeptide, after which a second, labeled antibody which binds to the first antibody is added. Other complement-anticomplement pairs are known in the art and include biotin/streptavidin.

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Diagnostic reagents as disclosed herein can be used *in vivo* or *in vitro*. In vitro diagnostic assays include assays of tissue and fluid samples. Assays for protein in serum, for example, may be used to detect metabolic abnormalities characterized by over- or under-production of the protein, such as cancers, immune system abnormalities, infections, organ failure, metabolic imbalances, inborn errors of metabolism and other disease states. Proteins of the present invention can also be used in the detection of circulating autoantibodies, which are indicative of autoimmune disorders. Those skilled in the art will recognize that conditions related to protein underexpression or overexpression may be amenable to treatment by therapeutic manipulation of the relevant protein level(s). Proteins in serum can be quantitated by known methods known in the art, which include the use of antibodies in a variety of formats. Non-antibody binding partners, such as ligand-binding receptor fragments (commonly referred to as "soluble receptors") can also be used.

In general, diagnostic methods employing oligonucleotide probes or primers comprise the steps of (a) obtaining a genetic sample from a patient; (b) incubating the genetic sample with an oligonucleotide probe or primer as disclosed above, under conditions wherein the probe or primer will hybridize to a complementary polynucleotide sequence, to produce a first reaction product; and (c) comparing the first reaction product to a control reaction product. A difference between the first reaction product and the control reaction product is indicative of a genetic abnormality in the patient. Genetic samples for use within such methods include genomic DNA, cDNA, and RNA. Suitable assay methods in this regard include molecular genetic techniques known to those in the art, such as restriction fragment length polymorphism (RFLP) analysis, short tandem repeat (STR) analysis employing PCR techniques, ligation chain reaction (Barany, PCR Methods and Applications 1:5-16, 1991), ribonuclease protection assays, and other genetic linkage analysis techniques known in the art (Sambrook et al., ibid.; Ausubel et. al., ibid.; A.J. Marian, Chest 108:255-65, 1995). Ribonuclease protection assays (see, e.g., Ausubel et al., *ibid.*, ch. 4) comprise the hybridization of an RNA probe to a patient RNA sample, after which the reaction product (RNA-RNA hybrid) is exposed to RNase. Hybridized regions of the RNA are protected from digestion. Within PCR assays, a patient genetic sample is incubated with a pair of oligonucleotide primers, and the region between the primers is amplified and recovered. Changes in size, amount, or sequence of recovered product are indicative of mutations in the patient. Another PCR-based technique that can be employed is single strand conformational polymorphism (SSCP) analysis (Hayashi, PCR Methods and Applications 1:34-38, 1991). Chromosomal localization data can be used to correlate AFP gene locations with known genetic disorders using, for example, 25 **OMIM**TM the Database, **Johns Hopkins** University, 2000 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM).

Relative chromosomal sublocalization shown in Table 11 was determined using the Draft Human Genome Browser (Kent, J., University of California Santa Cruz, http://genome.ucsc.edu/goldenPath/hgTracks.html) displaying the draft assembly of the July 17, 2000 version of the human genome. Table 11 also correlates AFP sequences with corresponding sequences in public databases by GenBank Accession Number, source clone ID number, and EST accession number. Also see Table 5, above.

		-	Ţ	Table 11			
AFP	GenBank Acc No	Source Clone ID No.	EST Acc. No.	Chr.	Band	Start	Stop
AFP127023	AP001155	RP11.594R10	*	8-	18012	35729370	35952786
AFP138504	AP001931	RP11-691N7	*	=	11p11.11	53438038	53888802
AFP138740	AC024059	RP11-79j21	AW580814	15	15q22.1	58185489	58481462
AFP138740	*	*	AW580814	15		58258653	58308652
AFP177000	AL118506	RP4-591C20	*	20	20q12	48950838	49160243
AFP178828	AC007686	CTD-2289B16;RP11- 116N21;RP11-7F17	*	14	14q23.3	62132030	62313415
AFP179530	AC011475	CTC-539A10	*	12	12912	41234876	41456630
AFP188135	AC013740	*	*	6	9q31.2	91150313	91361876
AFP194554	AC024888	RP11-901L	*	91	16q22.1	71944378	72167142
AFP199044	AC012180	RP11-31110	*	91	16q11.2	44574019	44904017
AFP199200	CNS01DV7	BAC-R-1070N10	*	14		82330266	82541053
AFP229269	AL161670	BAC-R-804M7	*	14	14921.3	46135365	46299284
AFP236718	AC010319	CTD-2521M24	*	61	19p13.3	4839920	5087628
AFP237679	601692	*	*	4	4p16.3	4521455	4544888
AFP244615	*	*	AI494556;AW85055 3	3	3q13.12	116466893	116517043
AFP249599	AL157714	RP11-541H12	*	-	1922-23.3	161893354	162136704
AFP250422	AC012046	RP11-312P12	*	10	10q22.1	81289799	81650062
AFP262739	AC005884	hRPK.264_B_14	*	17	17q23.3	64245127	64365313
AFP275580	AC016773	*	*	3	3q21.3	141329005	141513510
AFP277451	AC055822	RP11-707M3	*	8	8q13.3	75395740	75583383
AFP279267	*	*	A1566086	01	10q11.1	52859924	52861338
AFP280451	AL133355	RP11-541N10	*	01	10q24.32	115276306	115467187
AFP290397	#	*	AA421069	15	15q15.3	48427462	48427830
AFP293220	AC012476	RP11-532F12	*	15	15p11.1	17263661	17480097
AFP297548	*	#	W52728	11	11911	57918740	57927327
AFP306591	AQ079258	2366B9	AW118928	9	6p22.3	19812023	19812791
AFP313600	AC005037	NH0469M07	*	2	2q33.1	205320800	205511307
AFP324816	AC011687	RP11-15120	*	2	2p21	49054619	49249783
AFP325761	AC012485	RP11-5024	*	2	2p24.3	17554756	17765537

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20153358	44286594	126134148	138765140	128134589	3500834	4222465	143641730	1514256	59940397	19003942	173547400	70471703	16677574	50564907	60714738	108794286	137478427	#	77633569
19959493	44087441	125918909	138667522	128134250	3479999	4189155	142961410	1512179	88916865	1866311	173540737	70222075	16491516	50554924	60450247	108494503	137477811	*	77419530
14p11.1	17q21.2	12q24.23	1912-21.2	11q23.3	16p13.3	16p13.3		4p16.3	19913.33	8p21.3	5q33.1	16q22.1	19p13.13	6p21.1	13921.1	13q34	6q22.33	1p35.1-36.13	4q21.22
14	17	12		11	91	91	7	4	19	8	5	16	19	9	13	13	9	_	4
AI525611	*	*	*	AI253088	AI741157	*	AI133727	AI341602	*	AI814257	A1140615	*	*	AW583171		*	AA493506	*	*
BAC-R-407N17	CTD-2534121	*	3.28E+21	*	*	#	#	*	cosmid-R31181	*	*	RP11-502K10	CTB-SE10	#	RP11-342J4	RP11-391H12	*	RP5-1056L3	RP11-791G16
AL132639	AC015936	AC025740	AL022240	*	*	AC004235	*	*	AC006942	*	*	AC009131	AC008686	*	AL138695	AL136221	*	HS1056L3	AC067942
AFP326051	AFP345861	AFP347179	AFP372822	AFP374312	AFP375952	AFP395942	AFP404202	AFP404279	AFP413680	AFP436666	AFP448623	AFP460626	AFP477303	AFP501809	AFP545268	AFP561930	AFP71288	AFP74517	AFP93743

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If a mammal has an insufficiency of a protein of interest (due to, for example, a mutated or absent gene), the corresponding wild-type gene can be introduced into the cells of the mammal. In one embodiment, a gene encoding a protein of interest is introduced into the animal using a viral vector. Such vectors include an attenuated or defective DNA virus, such as, but not limited to, herpes simplex virus (HSV), papillomavirus, Epstein Barr virus (EBV), adenovirus, adenoassociated virus (AAV), and the like. Defective viruses, which entirely or almost entirely lack viral genes, are preferred. A defective virus is not infective after introduction into a cell. Use of defective viral vectors allows for administration to cells in a specific, localized area, without concern that the vector can infect other cells. Examples of particular vectors include, but are not limited to, a defective herpes simplex virus 1 (HSV1) vector (Kaplitt et al., Molec. Cell. Neurosci. 2:320-30, 1991); an attenuated adenovirus vector, such as the vector described by Stratford-Perricaudet et al. (J. Clin. Invest. 90:626-30, 1992); and a defective adeno-associated virus vector (Samulski et al., J. Virol. 61:3096-101, 1987; Samulski et al., J. Virol. 63:3822-28, 1989).

Within another embodiment, a gene of interest is introducted into an animal by liposome-mediated transfection ("lipofection") essentially as disclosed above. Lipofection can be used to introduce exogenous genes into specific organs.

A gene of interest can also be introduced into an animal for gene therapy as a naked DNA plasmid using the methods disclosed above.

In another embodiment, polypeptide-toxin fusion proteins or antibody/fragment-toxin fusion proteins may be used for targeted cell or tissue inhibition or ablation, such as in cancer therapy. Of particular interest in this regard are conjugates of an AFP protein and a cytotoxin, which can be used to target the cytotoxin to a tumor or other tissue that is undergoing undesired angiogenesis or neovascularization.

In another embodiment, AFP-cytokine fusion proteins or antibody/fragment-cytokine fusion proteins may be used for enhancing *in vitro* cytotoxicity (for instance, that mediated by monoclonal antibodies against tumor targets) and for enhancing *in vivo* killing of target tissues (for example, blood and bone marrow cancers). See, generally, Hornick et al., *Blood* 89:4437-4447, 1997). In general, cytokines are toxic if administered systemically. The described fusion proteins enable targeting of a cytokine to a desired site of action, such as a cell having binding sites for an AFP protein, thereby providing an elevated local concentration of cytokine. Polypeptides, antibodies, or receptors target an undesirable cell or tissue

(e.g., a tumor), and the fused cytokine mediates improved target cell lysis by effector cells. Suitable cytokines for this purpose include, for example, interleukin-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF).

In another embodiment, polypeptide-toxin fusion proteins or other binding partner-linked toxins may be used for targeted cell or tissue inhibition or ablation (for instance, to treat cancer cells or tissues). Target cells (i.e., those displaying a receptor for a polypeptide of interest) bind the polypeptide-toxin conjugate, which is then internalized, killing the cell. The effects of receptor-specific cell killing (target ablation) are revealed by changes in whole animal physiology or through histological examination. Thus, ligand-dependent, receptor-directed cyotoxicity can be used to enhance understanding of the physiological significance of a protein ligand. A preferred such toxin is saporin. Mammalian cells have no receptor for saporin, which is non-toxic when it remains extracellular. Alternatively, if the polypeptide of interest has multiple functional domains (i.e., an activation domain or a ligand binding domain, plus a targeting domain), a fusion protein including only the targeting domain may be suitable for directing a detectable molecule, a cytotoxic molecule or a complementary molecule to a cell or tissue type of interest. In instances where the domain-only fusion protein includes a complementary molecule, the anticomplementary molecule can be conjugated to a detectable or cytotoxic molecule. Such domain-complementary molecule fusion proteins thus represent a generic targeting vehicle for cell- or tissue-specific delivery of generic anti-complementarydetectable/cytotoxic molecule conjugates.

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The bioactive conjugates described herein can be delivered intravenously, intraarterially or intraductally, or may be introduced locally at the intended site of action.

For pharmaceutical use, the proteins of the present invention are formulated according to conventional methods. Routes of delivery include topical, mucosal, and parenteral, the latter including intravenous and subcutaneous delivery. Intravenous administration will be by bolus injection or infusion over a typical period of one to several hours. In general, pharmaceutical formulations will include a protein of the present invention in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water or the like. Formulations may further include one or more excipients, diluents, fillers, emulsifiers, preservatives, solubilizers, buffering agents, wetting agents, stabilizers, colorings, penetration enhancers, albumin to prevent protein loss on vial surfaces, etc. Topical formulations are typically provided as liquids, ointments, salves, gels, emulsions and the like. Methods of formulation are well known in the art and are disclosed, for example, in

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Remington: The Science and Practice of Pharmacy, Gennaro, ed., Mack Publishing Co., Easton, PA, 19th ed., 1995. Therapeutic doses will be determined by the clinician according to accepted standards, taking into account the nature and severity of the condition to be treated, patient traits, etc. Proteins of the present invention will generally be formulated to provide a dose of from 0.01 µg to 100 mg per kg patient weight per day, more commonly from 0.1 µg to 10 mg/kg/day, still more commonly from 0.1 µg to 1.0 mg/kg/day. Determination of dose is within the level of ordinary skill in the art. The proteins may be administered for acute treatment, over one week or less, often over a period of one to three days or may be used in chronic treatment, over several months or years. In general, a therapeutically effective amount is an amount sufficient to produce a clinically significant change in the targetted condition.

Within the laboratory research field, the proteins of the present invention can be used as molecular weight standards, or as standards in the analysis of cell phenotype, and as reagents for the study of cells, receptors, and other binding molecules. Such reagents will generally further comprise a second moiety, such as a label, binding partner, or toxin, that facilitates the detection of the protein when bound to its target. Many such systems are known in the art and are summarized above. Receptors and other cell-surface binding sites for proteins of the present invention can be identified by exposing a population of cells to a labelled protein under physiologic conditions, whereby the protein binds to the surface of the cell. Cells bearing receptors for a protein of interest can also be identified using the protein joined to a toxin, whereby receptor-bearing cells are killed by the toxin.

AFP proteins and antagonists thereof can be used as standards in assays of protein and protein inhibitors in both clinical and research settings. Such assays can comprise any of a number of standard formats, include radioreceptor assays and ELISAs. Protein standards can be prepared in labeled form using a radioisotope, enzyme, fluorophore, or other compound that produces a detectable signal. The proteins can be packaged in kit form, such kits comprising one or more vials containing the AFP protein and, optionally, a diluent, an antibody, a labeled binding protein, etc. Assay kits can be used in the research laboratory to detect protein and inhibitor activities produced by cultured cells or test animals.

Proteins of the present invention may also be used as protein and amino acid supplements, including hydrolysates. Specific uses in this regard include use as animal feed supplements and as cell culture components. Proteins rich in a particular amino acid can be used as a source of that amino acid.

Polynucleotides and polypeptides of the present invention will additionally find use as educational tools as a laboratory practicum kits for courses

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related to genetics and molecular biology, protein chemistry and antibody production and analysis. Due to their unique polynucleotide and polypeptide sequences, molecules of AFP protein or polynucleotide can be used as standards or as "unknowns" for testing purposes. For example, AFP polynucleotides can be used as aids in teaching students how to prepare expression constructs for bacterial, viral, and/or mammalian expression, including fusion constructs, wherein an AFP polynucleotide is the gene to be expressed; for determining the restriction endonuclease cleavage sites of the polynucleotides (which can be determined from the sequence using conventional computer software, such as MapDrawTM (DNASTAR, Madison, WI)); determining mRNA and DNA localization of AFP polynucleotides in tissues (e.g., by Northern and Southern blotting as well as polymerase chain reaction); and for identifying related polynucleotides and polypeptides by nucleic acid hybridization.

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AFP polypeptides can be used educationally as aids to teach preparation of antibodies; identifying proteins by Western blotting; protein purification; determining the weight of expressed AFP polypeptides as a ratio to total protein expressed; identifying peptide cleavage sites; coupling amino and carboxyl terminal tags; amino acid sequence analysis, as well as, but not limited to monitoring biological activities of both the native and tagged protein (i.e., receptor binding, signal transduction, proliferation, and differentiation) in vitro and in vivo. AFP polypeptides can also be used to teach analytical skills such as mass spectrometry, circular dichroism to determine conformation, in particular the locations of the disulfide bonds, x-ray crystallography to determine the three-dimensional structure in atomic detail, nuclear magnetic resonance spectroscopy to reveal the structure of proteins in solution. For example, a kit containing an AFP protein can be given to the student to analyze. Since the amino acid sequence would be known by the professor, the protein can be given to the student as a test to determine the skills or develop the skills of the student, the teacher would then know whether or not the student has correctly analyzed the polypeptide. Since every polypeptide is unique, the educational utility of zcub5 would be unique unto itself.

Antibodies that bind specifically to an AFP polypeptide can be used as a teaching aid to instruct students how to prepare affinity chromatography columns to purify the cognate polypeptide, cloning and sequencing the polynucleotide that encodes an antibody and thus as a practicum for teaching a student how to design humanized antibodies. The AFP polynucleotide, polypeptide or antibody would then be packaged by reagent companies and sold to universities so that the students gain skill in art of molecular biology. Because each polynucleotide and protein is unique, each polynucleotide and protein creates unique challenges and learning experiences for

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students in a lab practicum. Such educational kits containing an AFP polynucleotide, polypeptide or antibody are considered within the scope of the present invention.

The invention is further illustrated by the following non-limiting examples.

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EXAMPLES

Example 1

A protein of the present invention ("AFP") is produced in *E. coli* using a His₆ tag/maltose binding protein (MBP) double affinity fusion system as generally disclosed by Pryor and Leiting, *Prot. Expr. Pur.* 10:309-319, 1997. A thrombin cleavage site is placed at the junction between the affinity tag and AFP sequences.

The fusion construct is assembled in the vector pTAP98, which comprises sequences for replication and selection in *E. coli* and yeast, the *E. coli* tac promoter, and a unique Smal site just downstream of the MBP-His6-thrombin site coding sequences. The AFP cDNA is amplified by PCR using primers each comprising 40 bp of sequence homologous to vector sequence and 25 bp of sequence that anneals to the cDNA. The reaction is run using Taq DNA polymerase (Boehringer Mannheim, Indianapolis, IN) for 30 cycles of 94°C, 30 seconds; 60°C, 60 seconds; and 72°C, 60 seconds. One microgram of the resulting fragment is mixed with 100 ng of Smal-cut pTAP98, and the mixture is transformed into yeast to assemble the vector by homologous recombination (Oldenburg et al., *Nucl. Acids. Res.* 25:451-452, 1997). Ura⁺ transformants are selected.

Plasmid DNA is prepared from yeast transformants and transformed into *E. coli* MC1061. Pooled plasmid DNA is then prepared from the MC1061 transformants by the miniprep method after scraping an entire plate. Plasmid DNA is analyzed by restriction digestion.

E. coli strain BL21 is used for expression of AFP. Cells are transformed by electroporation and grown on minimal glucose plates containing casamino acids and ampicillin.

Protein expression is analyzed by gel electrophoresis. Cells are grown in liquid glucose media containing casamino acids and ampicillin. After one hour at 37°C, IPTG is added to a final concentration of 1mM, and the cells are grown for an additional 2-3 hours at 37°C. Cells are disrupted using glass beads, and extracts are prepared.

Example 2

Larger scale cultures of AFP transformants are prepared by the method of Pryor and Leiting (*ibid.*). 100-ml cultures in minimal glucose media containing casamino acids and 100 μ g/ml ampicillin are grown at 37°C in 500-ml baffled flasks to OD₆₀₀ \approx 0.5. Cells are harvested by centrifugation and resuspended in 100 ml of the same media at room temperature. After 15 minutes, IPTG is added to 0.5 mM, and cultures are incubated at room temperature (ca. 22.5°C) for 16 to 20 hours with shaking at 125 rpm. The culture is harvested by centrifugation, and cell pellets are stored at -70°C.

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Example 3

For larger-scale protein preparation, 500-ml cultures of *E. coli* BL21 expressing the AFP-MBP-His₆ fusion protein are prepared essentially as disclosed in Example 2. Cell pellets are resuspended in 100 ml of binding buffer (20 mM Tris, pH 7.58, 100 mM NaCl, 20 mM NaH₂PO₄, 0.4 mM 4-(2-Aminoethyl)-benzenesulfonyl fluoride hydrochloride [Pefabloc® SC; Boehringer-Mannheim], 2 μg/ml Leupeptin, 2 μg/ml Aprotinin). The cells are lysed in a French press at 30,000 psi, and the lysate is centrifuged at 18,000 x g for 45 minutes at 4°C to clarify it. Protein concentration is estimated by gel electrophoresis with a BSA standard.

Recombinant AFP fusion protein is purified from the lysate by affinity chromatography. Immobilized cobalt resin (Talon® resin; Clontech Laboratories, Inc., Palo Alto, CA) is equilibrated in binding buffer. One ml of packed resin per 50 mg protein is combined with the clarified supernatant in a tube, and the tube is capped and sealed, then placed on a rocker overnight at 4°C. The resin is then pelleted by centrifugation at 4°C and washed three times with binding buffer. Protein is eluted with binding buffer containing 0.2 M imidazole. The resin and elution buffer are mixed for at least one hour at 4°C, the resin is pelleted, and the supernatant is removed. An aliquot is analyzed by gel electrophoresis, and concentration is estimated. Amylose resin is equilibrated in amylose binding buffer (20 mM Tris-HCl, pH 7.0, 100 mM NaCl, 10 mM EDTA) and combined with the supernatant from the Talon resin at a ratio of 2 mg fusion protein per ml of resin. Binding and washing steps are carried out as disclosed above. Protein is eluted with amylose binding buffer containing 10 mM maltose using as small a volume as possible to minimize the need for subsequent concentration. The eluted protein is analyzed by gel electrophoresis and staining with Coomassie blue using a BSA standard, and by Western blotting using an anti-MBP antibody.

Example 4

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An expression plasmid containing all or part of a polynucleotide encoding AFP is constructed via homologous recombination. An AFP coding sequence comprising the ORF with 5' and 3' ends corresponding to the vector sequences flanking the insertion point is prepared by PCR. The primers for PCR each include from 5' to 3' end: 40 bp of flanking sequence from the vector and 17 bp corresponding to the amino or carboxyl termini from the open reading frame of AFP.

Ten µl of the 100 µl PCR reaction mixture is run on a 0.8% lowmelting-temperature agarose (SeaPlaque GTG®; FMC BioProducts, Rockland, ME) gel with 1 x TBE buffer for analysis. The remaining 90 µl of the reaction mixture is precipitated with the addition of 5 µl 1 M NaCl and 250 µl of absolute ethanol. The plasmid pZMP6, which has been cut with SmaI, is used for recombination with the PCR fragment. Plamid pZMP6 is a mammalian expression vector containing an expression cassette having the cytomegalovirus immediate early promoter, multiple restriction sites for insertion of coding sequences, a stop codon, and a human growth hormone terminator; an E. coli origin of replication; a mammalian selectable marker expression unit comprising an SV40 promoter, enhancer and origin of replication, a DHFR gene, and the SV40 terminator; and URA3 and CEN-ARS sequences required for selection and replication in S. cerevisiae. It was constructed from pZP9 (deposited at the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, under Accession No. 98668) with the yeast genetic elements taken from pRS316 (available from the American Type Culture Collection, 10801 University Boulevard, Manassas, VA, under Accession No. 77145), an internal ribosome entry site (IRES) element from poliovirus, and the extracellular domain of CD8 truncated at the C-terminal end of the transmembrane domain.

One hundred microliters of competent yeast (S. cerevisiae) cells are independently combined with 10 μl of the various DNA mixtures from above and transferred to a 0.2-cm electroporation cuvette. The yeast/DNA mixtures are electropulsed using power supply (BioRad Laboratories, Hercules, CA) settings of 0.75 kV (5 kV/cm), ∞ ohms, 25 μF. To each cuvette is added 600 μl of 1.2 M sorbitol, and the yeast is plated in two 300-μl aliquots onto two URA-D plates (1.8% agar in 2% D-glucose, 0.67% yeast nitrogen base without amino acids, 0.056% -Ura -Trp -Thr powder [made by combining 4.0 g L-adenine, 3.0 g L-arginine, 5.0 g L-aspartic acid, 2.0 g L-histidine, 6.0 g L-isoleucine, 8.0 g L-leucine, 4.0 g L-lysine, 2.0 g L-methionine, 6.0 g L-phenylalanine, 5.0 g L-serine, 5.0 g L-tyrosine, and 6.0 g L-valine], and 0.5% 200X tryptophan, threonine solution [3:0% L-threonine, 0.8% L-tryptophan in H₂O]) and incubated at 30°C. After about 48 hours, the Ura⁺ yeast

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transformants from a single plate are resuspended in 1 ml H_2O and spun briefly to pellet the yeast cells. The cell pellet is resuspended in 1 ml of lysis buffer (2% Triton X-100, 1% SDS, 100 mM NaCl, 10 mM Tris, pH 8.0, 1 mM EDTA). Five hundred microliters of the lysis mixture is added to an Eppendorf tube containing 300 μ l acid-washed glass beads and 200 μ l phenol-chloroform, vortexed for 1 minute intervals two or three times, and spun for 5 minutes in an Eppendorf centrifuge at maximum speed. Three hundred microliters of the aqueous phase is transferred to a fresh tube, and the DNA is precipitated with 600 μ l ethanol (EtOH), followed by centrifugation for 10 minutes at 4°C. The DNA pellet is resuspended in 10 μ l H₂O.

Transformation of electrocompetent *E. coli* host cells (Electromax DH10BTM cells; obtained from Life Technologies, Inc., Gaithersburg, MD) is done with 0.5-2 ml yeast DNA prep and 40 μl of cells. The cells are electropulsed at 1.7 kV, 25 μF, and 400 ohms. Following electroporation, 1 ml SOC (2% BactoTM Tryptone (Difco, Detroit, MI), 0.5% yeast extract (Difco), 10 mM NaCl, 2.5 mM KCl, 10 mM MgCl₂, 10 mM MgSO₄, 20 mM glucose) is plated in 250-μl aliquots on four LB AMP plates (LB broth (Lennox), 1.8% BactoTM Agar (Difco), 100 mg/L Ampicillin).

Individual clones harboring the correct expression construct for AFP are identified by restriction digest to verify the presence of the AFP insert and to confirm that the various DNA sequences have been joined correctly to one another. The inserts of positive clones are subjected to sequence analysis. Larger scale plasmid DNA is isolated using a commercially available kit (QIAGEN Plasmid Maxi Kit, Qiagen, Valencia, CA) according to manufacturer's instructions. The correct construct is designated pZMP6/AFP.

Recombinant protein is produced in BHK cells transfected with pZMP6/AFP. BHK 570 cells (ATCC CRL-10314) are plated in 10-cm tissue culture dishes and allowed to grow to approximately 50 to 70% confluence overnight at 37°C, 5% CO₂, in DMEM/FBS media (DMEM, Gibco/BRL High Glucose; Life Technologies), 5% fetal bovine serum (Hyclone, Logan, UT), 1 mM L-glutamine (JRH Biosciences, Lenexa, KS), 1 mM sodium pyruvate (Life Technologies). The cells are then transfected with pZMP6/AFP by liposome-mediated transfection using a 3:1 (w/w) liposome formulation of the polycationic lipid 2,3-dioleyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propaniminium-trifluoroacetate and the neutral lipid dioleoyl phosphatidylethanolamine in membrane-filtered water (LipofectamineTM Reagent; Life Technologies, Garithersburg, MD), in serum free (SF) media (DMEM supplemented with 10 mg/ml transferrin, 5 mg/ml insulin, 2 mg/ml fetuin, 1% L-glutamine and 1% sodium pyruvate). The plasmid is diluted into 15-ml tubes to a total final volume of 640 μl with SF media. 35 μl of the lipid mixture is

mixed with 605 µI of SF medium, and the resulting mixture is allowed to incubate approximately 30 minutes at room temperature. Five milliliters of SF media is then added to the DNA:lipid mixture. The cells are rinsed once with 5 ml of SF media, aspirated, and the DNA:lipid mixture is added. The cells are incubated at 37°C for five hours, then 6.4 ml of DMEM/10% FBS, 1% PSN media is added to each plate. The plates are incubated at 37°C overnight, and the DNA:lipid mixture is replaced with fresh 5% FBS/DMEM media the next day. On day 5 post-transfection, the cells are split into T-162 flasks in selection medium (DMEM + 5% FBS, 1% L-Gln, 1% NaPyr, 1 µM methotrexate). Approximately 10 days post-transfection, two 150-mm culture dishes of methotrexate-resistant colonies from each transfection are trypsinized, and the cells are pooled and plated into a T-162 flask and transferred to large-scale culture.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

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CLAIMS

We claim:

- 1. An isolated polypeptide comprising fifteen contiguous amino acid residues of a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422.
- 2. The isolated polypeptide of claim 1 wherein M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.
- 3. The isolated polypeptide of claim 1 or claim 2 which is from 15 to 2235 amino acid residues in length.
- 4. The isolated polypeptide of claim 3 which is operably linked via a peptide bond or polypeptide linker to a second polypeptide selected from the group consisting of maltose binding protein, an immunoglobulin constant region, a polyhistidine tag, and a peptide as shown in SEQ ID NO:423.
- 5. The isolated polypeptide of any of claims 1-4 comprising at least 30 contiguous residues of SEQ ID NO:M.
- 6. The isolated polypeptide of any of claims 1-5 comprising at least 47 contiguous residues of SEQ ID NO:M.
- 7. An isolated, mature protein encoded by a sequence selected from the group consisting of SEQ ID NO:N, wherein N is an odd integer from 1 to 421.
- 8. The protein of claim 7 wherein N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.
- 9. An isolated polynucleotide comprising a sequence of nucleotides as shown in SEQ ID NO:N, wherein N is an odd integer from 1 to 421.

- 10. The isolated polynucleotide of claim 9 wherein N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.
- 11. An expression vector comprising the following operably linked elements:
 - a transcription promoter;
- a DNA segment encoding a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422; and
 - a transcription terminator.
- 12. The expression vector of claim 11 wherein M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.
- 13. A cultured cell comprising the expression vector of claim 11 or claim 12.
- 14. A method of producing a polypeptide comprising culturing the cell of claim 13 under conditions whereby said sequence of nucleotides is expressed, and recovering said polypeptide.
 - 15. A polypeptide produced by the method of claim 14.
- 16. An isolated polynucleotide encoding a fusion protein, said protein comprising a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide.
- 17. An expression vector comprising the following operably linked elements:

- a transcription promoter;
- a DNA segment encoding a fusion protein, said protein comprising a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide; and a transcription terminator.
- 18. A cultured cell comprising the expression vector of claim 17, wherein the cell expresses the DNA segment and produces the encoded fusion protein.
- 19. A method of producing a protein comprising culturing the cell of claim 18 under conditions whereby said DNA segment is expressed, and recovering said second polypeptide.
- 20. An antibody that specifically binds to a protein selected from of the group consisting of SEQ ID NO:M, wherein M is an even integer from 2 to 422.

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Leu	Gly 210	Val	Ala	Val	Leu	Glu 215	Gly	Pro	Met	Tyr	Ala 220		Gly	Gly	His	
Asp 225	Gly	Trp	Ser	Tyr	Leu 230	Asn	Thr	Val	Glu	Arg 235	Trp	Asp	Pro	G1n	Ala 240	
Arg	Gln	Trp	Asn	Phe 245	Val	Ala	Thr	Met	Ser 250	Thr	Pro	Arg	Ser	Thr 255	Val	
Gly	Val	Ala	Va1 260	Leu	Ser	Gly	Lys	Leu 265	Tyr	Ala	Val	Gly	G1y 270	Arg	Asp	
Gly	Ser	Ser 275	Cys	Leu	Lys	Ser	Val 280	Glu	Cys	Phe	Asp	Pro 285	His	Thr	Asn	
Lys	Trp 290	Thr	Leu	Cys	Ala	G1n 295	Met	Ser	Lys	Arg	Arg 300	Gly	Gly	Val	Gly	•
Val 305	Thr	Thr	Trp	Asn	Gly 310	Leu	Leu	Tyr	Ala	Ile 315	Gly	Gly	His	Asp	Ala 320	
Pro	Ala	Ser	Asn	Leu 325	Thr	Ser	Arg	Leu	Ser 330	Asp	Cys	Val	Glu	Arg 335	Tyr	
Asp	Pro	Lys	Thr 340	Asp	Met	Trp	Thr	Ala 345	Val	Ala	Ser	Met	Ser 350	He	Ser	
Arg	Asp	A1 a 355	Val	Gly	Val	Cys	Leu 360	Leu	Gly	Asp	Lys	Leu 365	Tyr	Ala	Val	
Gly	Gly 370	Tyr	Asp	Gly	Gln	A1a 375	Tyr	Leu	Asn	Thr	Va1 380	Glu	Ala	Tyr	Asp	
385		Thr			390					Pro 395	Leu	Cys	Leu	Gly	Arg 400	
Ala	Gly	Ala	Cys	Val 405	Val	Thr	Val	Lys	Leu 410					-		
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		cgg Arg				_	_	_		-		-				48
-				9					TO					Ţ		

11 ·

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		-	•			ctc Leu				_		-		-		144
-	_					tac Tyr 55	-					-			-	192
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						att Ile							-			336
				_		cac His		_			_	-	_		_	384
				_	-	tcc Ser 135				-						432
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		_				agc Ser		-	_	_	_	_		-		576

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			_			 _	gag G1u				720
							ctg Leu				768
						_	gga Gly	-			816
							ccc Pro 285				864
							gag G1u				912
							ttt Phe				960
							atc Ile				1008
							ttc Phe				1056
							gtg Val 365				1104

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			ccc Pro					_	_	•			1248
		-	ctc Leu		_	_							1296
			gag Glu										1344
			cct Pro 455										1392
			gca Ala	-	-		-	-	_		_		1440
			gac Asp										1488
			cag Gln										1536
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Leu	Leu	Va1 275	Asp	Val	Phe	Asp	Gly 280	Pro	Ala	Ala	Gln	Pro 285	Ser	Leu	Gly
Pro	Thr 290	Pro	Glu	Glu	Ala	Phe 295	Leu	Ser	Pro	Gly	Pro 300	Glu	Asp	He	Gly
Pro 305	Pro	He	Pro	Glu	Ala 310	Asp	Glu	Leu	Leu	Asn 315	Lys	Phe	Val	Cys	Lys 320
Asn	Asn	Gly	Val	Leu 325	Phe	Glu	Asn	Gln	Leu 330	Leu	Gln	He	Gly	Va1 335	Lys
Ser	Glu	Phe	Arg 340	Gln	Asn	Leu	Gly	Arg 345	Met	Tyr	Leu	Phe	Tyr 350	Gly	Asn
Lys	Thr	Ser 355	Val	Gln	Phe	Gln	Asn 360	Phe	Ser	Pro	Thr	Val 365	Val	His	Pro
Gly	Asp 370	Leu	Gln	Thr	Gln	Leu 375	Ala	Val	Gln	Thr	Lys 380	Arg	Val	Ala	Ala
G1n 385	Val	Asp	Gly	Gly	A1 a 390	Gln	Val	Gln	Gln	Va1 395	Leu	Asn	He	Glu	Cys 400
Leu	Arg	Asp	Phe	Leu 405	Thr	Pro	Pro	Leu	Leu 410	Ser	Val	Arg	Phe	Arg 415	Tyr
Gly	Gly	Ala	Pro 420	Gln	Ala	Leu	Thr	Leu 425	Lys	Leu	Pro	Val	Thr 430	Į1е	Asn
Lys	Phe	Phe 435		Pro	Thr	Glu	Met 440	Ala	Ala	Gln	Asp	Phe 445	Phe	Gln	Arg
Trp	Lys 450	Gln	Leu	Ser	Leu	Pro 455	Gln	Gln	Glu	Ala	G1n 460	Lys	He	Phe	Lys
A1 a 465	Asn	His	Pro	Met	Asp 470	Ala	Glu	Val	Thr	Lys 475	Ala	Lys	Leu	Leu	G1y 480
Phe	Gly	Ser	Ala	Leu 485	Leu	Asp	Asn	Val	Asp 490	Pro	Asn	Pro	Glu	Asn 495	Phe
Val	Gly	Ala	Gly 500	Пe	Пе	Gln	Thr	Lys 505	Ala	Leu	Gln	Val	Gly 510	Cys	Leu
Leu	Arg	Leu 515	Glu	Pro	Asn	Ala	G1n 520	Ala	Gln	Met	Tyr	Arg 525	Leu	Thr	Leu
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PCT/US00/29052

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_	_	-	•	•	gct Ala					-				52	28
					ggt Gly									57	'6
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Ser	Ser	Asp	Arg	Cys 165	Ala	Leu	Ser	Ser	Pro 170	Ser	Leu	Ala	Phe	Thr 175	Pro	
Pro	He	Lys	Thr 180	Leu	Gly	Thr	Pro	Thr 185	Gln	Pro	Gly	Ser	Thr 190	Pro	Arg	
Пе	Ser	Thr 195	Met	Arg	Pro	Leu	A1a 200	Thr	Ala	Tyr	Lys	Ala 205	Ser	Thr	Ser	
Asp	Tyr 210	Gln	Val	He	Ser	Asp 215	Arg	Gln	Thr	Pro	Lys 220	Lys	Asp	Glu	Ser	
Leu 225	Val	Ser	Lys	Ala	Met 230	Glu	Tyr	Met	Phe	G1y 235	Trp					
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			tcc Ser													144
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			gag Glu					_							_	240

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_			•	•	-		-					_	aaa Lys 110	_		336
		-		-			-				_		atg Met	_	_	384
_	-		-									_	gag Glu		-	432
				-			_				•	٠.	aat Asn	_		480
													aaa Lys	-		528
			-		_					-	-	-	aaa Lys 190	-		576
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	aag Lys 210	tgg Trp	taa *													636
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Asp	Gln	Met 35	Ser	Asn	Glu	Glu	Leu 40	Tyr	Asp	Asn	Leu	Leu 45	Ser	Cys	Ser	
His	Arg 50	Thr	His	Val	Val	A1a 55	Arg	Lys	Met	Tyr	Lys 60	Пe	Leu	Asp	Leu	
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		•	100	Val				105					110			
		115		Leu			120			_	·	125				
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				Ser 165					170					175		
			180	Phe				185					190	-		
		195	Lys	Asp	Tyr	Leu	G1n 200	He	Leu	Arg	Pro	Asn 205	He	He	Lys	
Asn	Lys 210	irp														
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								. •				9	••		•	

			20			25				30		
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		gca Ala										192
		cac His										240
		ccg Pro										288
		ctg Leu									-	336
		gac Asp 115										384
		gga Gly					_	_	•	_	 -	432
٠		ttc Phe										480
		tct Ser										528
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Pro Glu Ser Ala Pro Gln Asn Gly Pro Ser Pro Met Ala Ala Leu Met 35 40 45

Ser Val Ala Asp Thr Leu Gly Thr Ala His Ser Pro Lys Asp Gly Ser 50 55 60

Ser Val His Ser Thr Thr Ala Ser Ala Arg Arg Asn Ser Ser Ser Pro 65 70 75 80

Val Ser Pro Ala Ser Val Pro Gly Gln Arg Arg Leu Ala Ser Arg Asn 85 90 95

Gly Asp Leu Asn Leu Gln Val Ala Pro Pro Pro Pro Ser Ala His Pro
100 105 110

Gly Met Asp Gln Val His Pro Gln Asn Ile Pro Asp Ser Pro Met Ala 115 120 125

Asn Ser Gly Pro Leu Cys Cys Thr Ile Cys His Glu Arg Leu Glu Asp 130 135 140

Thr His Phe Val Gln Cys Pro Ser Val Pro Ser His Lys Phe Cys Phe 145 150 155 160

Pro Cys Ser Arg Glu Ser Ile Lys Ala Gln Gly Ala Thr Gly Glu Val 165 170 175

Tyr Cys Pro Ser Gly Glu Lys Cys Pro Leu Val Gly Ser Asn Val Pro 180 185 190

Trp Ala Phe Met Gln Gly Glu Ile Ala Thr Ile Leu Ala Gly Asp Val 195 200 205

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							tca Ser			3	36
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_	_		gtg Val			-	-				_		•			144
	-		gag Glu	_		-	-									192
		-	ctg Leu	_		-					-	_				240
			tcc Ser	_				_	_					_	_	288
			gag Glu 100								-	_	-	-	_	336
			gag G1u										_			384
			gct Ala													432
			ctc Leu		_		-	_	-	-	_		_			480
			gca Ala			-	_			-		-		-		528
			agc Ser		_	-				-			-	-		576

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Leu	Tyr	Pro	Ala	Tun	^	_										
Lys			20	Tyl.	Ser	Ser	Tyr	Lys 25	Ala	Val	Lys	Thr	-		Val	
	Glu	Tyr 35	20					25			•	Phe	30	Asn		
Thr		35	20 Va1	Lys	Trp	Met	Met 40	25 Tyr	Ala	He	Val	Phe 45	30 Ala	Asn Phe	Phe	
	Thr 50	35 Ala	20 Val Glu	Lys Thr	Trp Leu	Met Thr 55	Met 40 Asp	25 Tyr Ile	Ala Trp	Ile Leu	Val Ser 60	Phe 45 Trp	30 Ala Phe	Asn Phe Pro	Phe Phe	
Tyr 65	Thr 50 Phe	35 Ala Glu	20 Val Glu Leu	Lys Thr Lys	Trp Leu Ile 70	Met Thr 55 Ala	Met 40 Asp Phe	25 Tyr Ile Val	Ala Trp Val	Ile Leu Trp 75	Val Ser 60 Leu	Phe 45 Trp Leu	30 Ala Phe Ser	Asn Phe Pro Pro	Phe Phe Tyr 80	
Tyr 65 Thr	Thr 50 Phe Lys	35 Ala Glu Gly	20 Val Glu Leu Ser	Lys Thr Lys Ser 85	Trp Leu Ile 70 Val	Met Thr 55 Ala Leu	Met 40 Asp Phe Tyr	25 Tyr Ile Val Arg	Ala Trp Val Ile Lys	Ile Leu Trp 75 Phe	Val Ser 60 Leu Val	Phe 45 Trp Leu His	30 Ala Phe Ser Pro	Asn Phe Pro Pro Thr 95	Phe Phe Tyr 80 Leu	
Tyr 65 Thr Ser	Thr 50 Phe Lys Asn	35 Ala Glu Gly Lys	20 Val Glu Leu Ser Glu 100	Lys Thr Lys Ser 85 Lys	Trp Leu Ile 70 Val Glu	Met Thr 55 Ala Leu Ile	Met 40 Asp Phe Tyr Asp	25 Tyr Ile Val Arg Glu 105	Ala Trp Val Ile Lys 90	Ile Leu Trp 75 Phe Ile	Val Ser 60 Leu Val	Phe 45 Trp Leu His	30 Ala Phe Ser Pro Ala 110	Asn Phe Pro Pro Thr 95 Arg	Phe Phe Tyr 80 Leu Asp	

Ser Glu Lys Leu Arg Ser Phe Ser Met Gln Asp Leu Thr Leu Ile Arg

145 150 155 160 Asp Glu Asp Ala Leu Pro Leu Gln Arg Pro Asp Gly Arg Leu Arg Pro 165 170 Ser Pro Gly Ser Leu Leu Asp Thr Ile Glu Asp Leu Gly Asp Asp Pro 185 Ala Leu Ser Leu Arg Ser Ser Thr Asn Pro Ala Asp Ser Arg Thr Glu 195 200 -205 Ala Ser Glu Asp Asp Met Gly Asp Lys Ala Pro Lys Arg Ala Lys Pro 215 220 Ile Lys Lys Ala Pro Lys Ala Glu Pro Leu Ala Ser Lys Thr Leu Lys 230 235 Thr Arg Pro Lys Lys Lys Thr Ser Gly Gly Gly Asp Ser Ala 245 250 <210> 17 <211> 408 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(408) <221> misc feature <222> (1)...(408) <223> n = A.T.C or G<400> 17 atg gcc cat agg ggc gtg tca gct gtg gtc gtg gga gct gac cgc gtg 48 Met Ala His Arg Gly Val Ser Ala Val Val Val Gly Ala Asp Arg Val 1 5 10 15 96 gtt gcc aac ggn gac aca gcc aac aag gtg ggc acc tac cag ctg gcc Val Ala Asn Xaa Asp Thr Ala Asn Lys Val Gly Thr Tyr Gln Leu Ala 20 30 att gtc gcc aag cac cat ggc att ccc ttc tac gtg gct gcc ccc agc 144 Ile Val Ala Lys His His Gly Ile Pro Phe Tyr Val Ala Ala Pro Ser 35 40 45 tct tca tgt gac ctc cgt ctg gag acc ggc aag gag atc att att gaa 192 Ser Ser Cys Asp Leu Arg Leu Glu Thr Gly Lys Glu Ile Ile Ile Glu 50 55 60

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-						atc Ile			-	•		-		•		336
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		•	gga Gly		_	atg Met 135	taa *									408
	- 6	10.	10													
		210>														
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Пe	Val	A1 a 35		His	His	Gly	11e 40		Phe	Tyr	Val	A1a 45		Pro	Ser	
Ser	Ser 50	Cys	Asp	Leu	Arg	Leu 55	Glu	Thr	Gly	Lys	Glu 60	He	He	He	Glu	
Glu 65	Aṛg	Pro	Gly	Gln	G1u 70	Leu	Thr	Asp	Val	Asn 75		Val	Arg	He	Ala 80	
	Pro	Gly	He	G1y 85	Val	Trp	Asn	Pro	A1 a 90		Asp	Val	Thr	Pro 95		

Asp	Leu	Ile	Thr 100	Gly	Gly	Пе	Пе	Thr 105	Glu	Leu	Gly	Val	Phe 110	Ala	Pro	
G1u	Glu	Leu 115	Arg	Thr	Ala	Leu	Thr 120	Thr	Thr	Пe	Ser	Ser 125		Asp	Gly	
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	-				-	_					ctt Leu	•				528
											ctg Leu				-	576
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							-			-	ttt Phe 220				-	672
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														999 Gly		144
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											_		-	ttt Phe		240
														ccc Pro 95		288
							_		_		_		-	agc Ser		336
gag	ttt	gaa	tcc	cag	agc	cct	agg	tat	gaa	ccc	caa	agc	cct	ggc	tat	384

Glu		Glu 115	Ser	Gln	Ser	Pro	Arg 120	Tyr	Glu	Pro	Gln	Ser 125	Pro	Gly	Tyr	
			_		ggg Gly		-			_				_		432
					gaa Glu 150											480
	-		-	-	caa G1n	-				-	-				-	528
	-			_	gaa G1u	-	-						_		-	576
					ttc Phe											624
-	-				cca Pro				-				-	_	_	672
		_			gag G1u 230	_		_			_					720
					ggt Gly						-				-	768
					atc Ile				-		_	-				816
			-		cag Gln		-	-						-		864
tac	aaa	tgt	gag	gtc	tgc	agc	aag	gcc	ttc	tcc	cag	agc	tct	gac	ctc	912

Tyr	Lys 290	Cys	Glu	Val	Cys	Ser 295	Lys	Ala	Phe	Ser	G1n 300	Ser	Ser	Asp	Leu	
	Lys	cac His														960
		ggc Gly														1008
		cac His														1056
		ggc Gly 355										-			_	1104
cac His	gag G1u 370	cgg Arg	ccc Pro	tac Tyr	agc Ser	tgc Cys 375	acc Thr	gag G1u	tgc Cys	ggc Gly	aag Lys 380	tgc Cys	tat Tyr	agc Ser	cag Gln	1152
		tcc Ser														1200
		tgt Cys														1248
		cat His														1296
gag Glu	tgc Cys	ggc G1y 435	aag Lys	cgc Arg	ttt Phe	ggc Gly	cag Gln 440	agc Ser	tcg Ser	gtg Val	ctg Leu	gcc Ala 445	atc Ile	cac His	gcc Ala	1344
cgc Arg	acc Thr 450	cac His	ctg Leu	cca Pro	ggc Gly	cgc Arg 455	acc Thr	tac Tyr	agc Ser	tgc Cys	ccc Pro 460	gac Asp	tgc Cys	ggc Gly	aag Lys	1392
acc	ttc	aat	cgc	tcc	tcc	act	ctc	atc	cag	cac	cag	cgc	tcc	cac	acg	1440

Thr Phe Asn Arg Ser Ser Thr Leu Ile Gln His Gln Arg Ser His Thr 465 470 475 480	
ggc gag cgg ccc tac agg tgc gcc gtg tgc ggc aag ggc ttc tgc cgc Gly Glu Arg Pro Tyr Arg Cys Ala Val Cys Gly Lys Gly Phe Cys Arg 485 490 495	1488
tcc tcc acg ctt ctg cag cat cac cgg gtc cac agt ggc gag cgg cct Ser Ser Thr Leu Leu Gln His His Arg Val His Ser Gly Glu Arg Pro 500 505 510	1536
tac aag tgc gat gac tgc gga aag gcc ttc tcc cag agc tcc gac ctc Tyr Lys Cys Asp Asp Cys Gly Lys Ala Phe Ser Gln Ser Ser Asp Leu 515 520 525	1584
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Glu	Pro 130	Arg	Ser	Pro	Gly	Tyr 135	Glu	Pro	Arg	Ser	Pro 140	Gly	Tyr	Glu	Ser
G1u 145	Ser	Ser	Arg	Tyr	Glu 150	Ser	Gln	Asn	Thr	Glu 155	Leu	Lys	Thr	Gln	Ser 160
Pro	Glu	Phe	Glu	Ala 165	Gln	Ser	Ser	Lys	Phe 170	Gln	Glu	Gly	Ala	Glu 175	Met
			180		Glu			185					190		
		195			Phe		200					205			
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225					G1u 230					235		_			240
				245	Gly				250					255	
			260		Ile			265					270		
		275			Gln		280					285	•		
	290				Cys	295			•		300			•	
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				325	Phe				330					335	
			340		Gln			345					350		
		355			Ser		360					365			
	370				Ser	375					380				
385					Ser 390					395					400
				405	Cys				410					415	
He	Pro	His	A1a 420	Arg	Ser	His	Ala	Arg 425	Glu	Lys	Pro	Phe	Lys 430	Cys	Pro
		435			Phe		440					445			
Arg	Thr	His	Leu	Pro	Gly	Arg	Thr	Tyr	Ser	Cys	Pro	Asp	Cys	Gly	Lys

	450					455					460					
Thr 465	Phe	Asn	Arg	Ser	Ser 470	Thr	Leu	Пe	Gln	His 475	Gln	Arg	Ser	His	Thr 480	
Gly	Glu	Arg	Pro	Tyr 485	Arg	Cys	Ala	Val	Cys 490	Gly	Lys	Gly	Phe	Cys 495	Arg	
Ser	Ser	Thr	Leu 500	Leu	Gln	His	His	Arg 505	Val	His	Seņ	Gly	G1u 510	Arg	Pro	
Tyr	Lys	Cys 515	Asp	Asp	Cys	Gly	Lys 520	Ala	Phe	Ser	Gln	Ser 525	Ser	Asp	Leu	
He	Arg 530	His	Gln	Arg	Thr	His 535	Ala	Ala	Gly	Arg	Arg 540					
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												gag Glu				96
			Pro									atc Ile 45		_		144
										-		gtg Val	_			192
												ctg Leu				240
			-						-			ttt Phe	-	-		288

85 90 95 aga atc atc acc acg gcg gtg gac aag cgg gtc aat gac ctt ttc cgc 336 Arg Ile Ile Thr Thr Ala Val Asp Lys Arg Val Asn Asp Leu Phe Arg 100 105 110 atc atc cca ggc att ggg aac ttt ggc gac cgc tac ttt ggg aca gac 384 Ile Ile Pro Gly Ile Gly Asn Phe Gly Asp Arg Tyr Phe Gly Thr Asp 115 120 125 gcg gtc ccc gat ggc agt gac gag gag gaa gtg gcc tac acg ggt tag 432 Ala Val Pro Asp Gly Ser Asp Glu Glu Glu Val Ala Tyr Thr Gly * 130 135 <210> 24 <211> 143 <212> PRT <213> Homo sapiens <400> 24 Met Glu Pro Ala Leu Arg Ala Val Cys Lys Asp Val Arg Ile Gly Thr Ile Leu Ile Gln Thr Asn Gln Leu Thr Gly Glu Pro Glu Leu His Tyr 20 25 Leu Arg Leu Pro Lys Asp Ile Ser Asp Asp His Val Ile Leu Met Asp Cys Thr Val Ser Thr Gly Ala Ala Ala Met Met Ala Val Arg Val Leu Leu Asp His Asp Val Pro Glu Asp Lys Ile Phe Leu Leu Ser Leu Leu 75 Met Ala Glu Met Gly Val His Ser Val Ala Tyr Ala Phe Pro Arg Val 90 Arg Ile Ile Thr Thr Ala Val Asp Lys Arg Val Asn Asp Leu Phe Arg 105 Ile Ile Pro Gly Ile Gly Asn Phe Gly Asp Arg Tyr Phe Gly Thr. Asp 120 Ala Val Pro Asp Gly Ser Asp Glu Glu Glu Val Ala Tyr. Thr Gly 130 135 140 <210> 25 <211> 912 <212> DNA

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ctc a Leu T															9	96
cgc a Arg L									_	_					1	44
ttc g Phe V															19	92
ctg c Leu P 65					-	-	-	-	_	-			_		24	40
gac a Asp A															. 2	88
gtg c Val L											-			_	3:	36
aag a Lys M	let I											_	-		31	84
tgt g Cys V 1															43	32
ggg a							tac			att	ctc	tcc	ctc	tca	48	80

Gly Arg Arg Asn Tyr Arg Phe Phe Tyr Ala Phe Ile Leu Ser Leu Ser

145	150	155	160
		gtc acc cac ctg Val Thr His Leu	
Arg Ala Gln G		ctg aag gag aca Leu Lys Glu Thr 190	
		tcc atc tgg tcc Ser Ile Trp Ser 205	
		gcc tcc aac ctg Ala Ser Asn Leu 220	
		aag agg ggc ggt Lys Arg Gly Gly 235	
		atc acc aac tgc Ile Thr Asn Cys	
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<211> 303

<212> PRT

<213> Homo sapiens

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<210> 27

<211> 795

<212> DNA

<213> Homo sapiens

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							-	-				-		atc Ile		96
							_			-		-	_	aat Asn		144
				_	-			-	_			_		gaa Glu		192
													-	gaa Glu		240
														aaa Lys 95		288
										-	-			ata Ile	-	336
														gat Asp		384
						-	-	-		-				gtt Val		432

	130					135					140					
-			-		cct Pro 150	_			-	-			_			480
	-		-		act Thr					_	-	-	_	_	_	528
					aca Thr											576
		-	_	_	gct Ala					_			_		_	624
-				_	act Thr											672
-					aca Thr 230	-		_		_	_	-			-	720
-			-	_	gaa Glu		_	-	-	-	-	-	_			768
		-		_	ctt Leu			taa *								795
	<'a	210> 211> 212> 213>	264 PRT	o saj	oiens	S										
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Gln	Leu	Ala	Gly	Leu 165	Thr	Leu	Leu	Thr	Asn 170	Met	Thr	Val	Thr	Asn 175	Asp		
			atg Met 180								_		-				576
			aat Asn														624
			gaa Glu			_	_		-				-	-		ı	672
			tca Ser							_	_	tag *					711
	<2 <2 <2	210> 211> 212> 213>	236 PRT Homo	sap	oiens	5		-									
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_	Ala	Gly	A1a 20	_	Tyr	Cys	Пе	Tyr 25		Leu	Thr	Arg	Gly 30		Arg		
Arg	G1y	Asp 35	Arg					_		Ser	_	Ser 45	Ala	Glu	Asp		
Leu	Thr 50	Asp	Gly	Ser	Tyr	Asp 55	Asp	Val	Leu	Asn	A1 a 60	Glu	Gln	Leu	Gln		
Lys 65	Leu	Leu	Tyr	Leu	Leu 70	Glu	Ser	Thr	Glu	Asp 75	Pro	Val	He	He	Glu 80		
Arg	Ala	Leu	He	Thr 85	Leu	Gly	Asn	Asn	A1a 90	Ala	Phe	Ser	Val	Asn 95	Gln		
Ala	He	Ile	Arg 100	Glu	Leu	Gly	Gly	Ile 105	Pro	He	Val	Ala	Asn 110	Lys	He		
Asn	His	Ser 115	Asn	Gln	Ser	Ile	Lys 120	Glu	Lys	Ala	Leu	Asn 125	Ala	Leu	Asn		
Asn	Leu 130	Ser	Val	Asn	Val	Glu 135	Asn	Gln	He	Lys	Ile 140	Lys	Пe	Tyr	He		

Ser 145	Gln	Val	Cys	Glu	Asp 150	Val	Phe	Ser	Gly	Pro 155	Leu	Asn	Ser	Ala	Val 160	
Gln	Leu	Ala	Gly	Leu 165	Thr	Leu	Leu	Thr	Asn 170	Met	Thr	Val	Thr	Asn 175		
His	Gln	His	Met 180	Leu	His	Ser	Tyr	I le 185	Thr	Asp	Leu	Phe	Gln 190		Leu	
Leu	Thr	Gly 195	Asn	Gly	Asn	Thr	Lys 200	Val	Gln	Val	Leu	Lys 205	Leu	Leu	Leu	
Asn	Leu 210	Ser	Glu	Asn	Pro	Ala 215	Met	Thr	Glu	Gly	Leu 220	Leu	Arg	Ala	Gln	
Va1 225	Asp	Ser	Ser	Phe	Leu 230	Ser	Leu	Met	Thr	A1a 235	Thr					
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	ccg Pro															90
	gtc Val															144
	ctg Leu 50															192
	tgg Trp															240
cag	gag	tgg	ctg	gcg	gct	gtg	ggc	gat	gac	tat	gct	gct	gtg	gtc	tgg	288

Gln	Glu	Trp	Leu	A1a 85	Ala	Val	Gly	Asp	Asp 90	Tyr	Ala	Ala	Val	Va1 95	Trp	
	cct Pro									-	-				•	336
	tgg Trp									_			_	-	-	384
	ctc Leu 130									_			-		-	432
	aca Thr	-			-				_		-				-	480
	cag Gln				-				_	-	-		_			528
	tcc Ser									_				-	-	576
	gcc Ala															624
cgt Arg	gtc Val 210	ccc Pro	atg Met	gtc Val	cac His	tcc Ser 215	acc Thr	ttc Phe	ctt Leu	gca Ala	tcc Ser 220	ctg Leu	cgg Arg	gct Ala	gaa Glu	672
	gca Ala							_							~ ~	720
	ttc Phe															768
gtc	tcc	gtc	cac	gtg	tgc	aat	gag	cac	cgt	tat	999	tac	atg	aat	gtg	816

Val	Ser	Val	His 260	Val	Cys	Asn	Glu	His 265	Arg	Tyr	Gly	Tyr	Met 270	Asn	Val	
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					gca Ala						-	-	_	_		912
					ccc Pro 310										-	960
					agc Ser											1008
					tgg Trp											1056
					atg Met											1104
					ggc Gly		_	-					-		-	1152
	_		-		ggc Gly 390	-			_						_	1200
					ggc Gly											1248
					aac Asn											1296
gat	gtg	gag	gca	gag	aaa	ctg	tct	tgg	gac	ctg	atc	tac	ctc	gga	cgg	1344

Asp	Val	G1u 435	Ala	Glu	Lys	Leu	Ser 440	Trp	Asp	Leu	Ile	Tyr 445	Leu	Gly	Arg	
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				ggg Gly												1440
				cgc Arg 485												1488
				gag Glu												1536
				gca Ala												1584
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				acg Thr												1680
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<211> 578

<212> PRT

<213> Homo sapiens

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Met Leu Ala Ser Leu Trp Glu Met Glu Ile Ser Gly Arg Val Val Asp
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Ala Val Asp Gly Trp Met Leu Asn Ser Ser Ala Ile Arg Asn Leu Gly
                            360
Val Asp Leu Leu Pro Gly Tyr Gln Asp Pro Tyr Ser Gly Arg Thr Leu
                        375
                                            380
Thr Lys Gly Glu Val Gly Cys Phe Leu Ser His Tyr Ser Ile Trp Glu
                    390
                                        395
Glu Val Val Ala Arg Gly Leu Ala Arg Val Leu Val Phe Glu Asp Asp
                405
                                    410
Val Arg Phe Glu Ser Asn Phe Arg Gly Arg Leu Glu Arg Leu Met Glu
                                425
           420
Asp Val Glu Ala Glu Lys Leu Ser Trp Asp Leu Ile Tyr Leu Gly Arg
                            440
Lys Gln Val Asn Pro Glu Lys Glu Thr Ala Val Glu Gly Leu Pro Gly
                        455
                                            460
Leu Val Val Ala Gly Tyr Ser Tyr Trp Thr Leu Ala Tyr Ala Leu Arg
                    470
                                        475
Leu Ala Gly Ala Arg Lys Leu Leu Ala Ser Gln Pro Leu Arg Arg Met
                                    490
Leu Pro Val Asp Glu Phe Leu Pro Ile Met Phe Asp Gln His Pro Asn
           500
                                505
Glu Gln Tyr Lys Ala His Phe Trp Pro Arg Asp Leu Val Ala Phe Ser
                            520
Ala Gln Pro Leu Leu Ala Ala Pro Thr His Tyr Ala Gly Asp Ala Glu
                        535
                                            540
Trp Leu Ser Asp Thr Glu Thr Ser Ser Pro Trp Asp Asp Ser Gly
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Trp Thr
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<211> 1152

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

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Met	Tyr	Val	Leu 180	Gly	Met	Ala	Glu	G1u 185	Phe	Lys	Gly	Glu	I le 190	Ala	Val	
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_						-	_	_	_	-		-	•	atc Ile		672
-									-			-		act Thr		720
					_					-	_			gaa Glu 255		768
	-	-		_										gat Asp		816
			-			-	_	_	-	_			-	tca Ser		864
														cca Pro		912
														gac Asp		960
	_	-	-	•	_		-			_			-	ttt Phe 335	_	1008
			_	-			_				_	_		agc Ser	_	1056
ggt	999	aat	gtc	gga	tat	gga	gag	cct	tct	gat	cag	gca	gat	gtg	gtg	1104

Gly Gly Asn Val Gly Tyr Gly Glu Pro Ser Asp Gln Ala Asp Val Val 355 360

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235

240

Asn	Phe	Va1	He	Asp 245	Glu	Asn	He	Leu	Lys 250	Glu	Glu	Gly	He	G1u 255	Asn	
Phe	Asp	Val	Tyr 260	Ala	Ile	Lys	Pro	Gly 265	His	Pro	Leu	Gln	Pro 270		Phe	
Phe	Leu	Asp 275	Glu	Tyr	Pro	Glu	A1a 280		Ser	Lys	Lys	Val 285		Ser	Thr	
Gly	Ala 290		Pro	Glu	Phe	Lys 295		Glu	Lys	Leu	G1n 300		G1n	Pro	Lys	
Pro 305	Arg	Ser	Gly	Ala	Val 310	Glu	Glu	Thr	Phe	Arg 315	Пe	Val	Lys	Asp	Ser 320	
Leu	Ser	Asp	Asp	Va1 325	Val	Lys	Ala	Thr	G1n 330	Ala	Ile	Tyr	Leu	Phe 335		
Leu	Ser	Gly	G1u 340	Asp	Gly	Gly	Thr	Trp 345	Phe	Leu	Asp	Leu	Lys 350	Ser	Lys	
Gly	Gly	Asn 355	Val	Gly	Tyr	Gly	G1u 360	Pro	Ser	Asp	Gln	A1a 365	Asp	Val	Val	
Met	Ser 370	Met	Thr	Thr	Asp	Asp 375	Phe	Val	Lys	Met	Phe 380	Ser	Gly	Asn		
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	tgc Cys															96
	aac Asn														-	144

	gtg Val 50												192
	tac Tyr	_	-		_		_		-				240
	ctg Leu										_	-	288
_	tac Tyr	_	_		-	-	 -						336
	ctc Leu							-		 -	-		384
	aat Asn 130					_	-		_	 			432
	ggt Gly												480
	ttc Phe												528
	ctc Leu												576
	gag Glu												624
	ctc Leu 210												672

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												gtc Val 255		768
-	-	_	-	-	_		_		_	•	•	gcc Ala		816
												tcc Ser		864
										-	-	ggc Gly		912
												tgg Trp		960
												ctc Leu 335		1008
												atg Met		1056
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												gcc Ala		1200

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agc tgg gca ggg ctg ctc ctc tac ctg tgg acc ctg gta gcc cca ctc Ser Trp Ala Gly Leu Leu Leu Tyr Leu Trp Thr Leu Val Ala Pro Leu 435 440 445	1344
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um		uly	Phe	irp	rne		Lys	PILE	reu	He		VdI	ыу	Leu	m
	130					135	_		_		140				
	Gly	Ala	Phe	Tyr		Pro	Asp	Gly	Ser		Thr	Asn	He	Trp	
145					150					155					160
Tyr	Phe	Gly	Val	Val 165	Gly	Ser	Phe	Leu	Phe 170	Ile	Leu	He	Gln	Leu 175	Val
Leu	Leu	Ile	Asp 180	Phe	Ala	His	Ser	Trp 185		Gln	Arg	Trp	Leu 190	Gly	Lys
Ala	Glu	G1u 195	Cys	Asp	Ser	Arg	Ala 200	Trp	Tyr	Ala	Gly	Leu 205	Phe	Phe	Phe
Thr	Leu 210	Leu	Phe	Tyr	Leu	Leu 215	Ser	He	Ala	Ala	Val 220	Ala	Leu	Met	Phe
Met 225	Tyr	Tyr	Thr	Glu	Pro 230	Ser	Gly	Cys	His	G1u 235	Gly		Val	Phe	I1e 240
Ser	Leu	Asn	Leu	Thr 245	Phe	Cys	Val	Cys	Va1 250	Ser	Пe	Ala	Ala	Va1 255	Leu
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G1u 305	Thr	Val	Val	Ala	Gly 310	Pro	Glu	Gly	Tyr	G1u 315	Thr	Gln	Trp	Trp	Asp 320
Ala	Pro	Ser	He	Val 325	Gly	Leu	Пe	He	Phe 330	Leu		Cys	Thr	Leu 335	Phe
Ile	Ser	Leu	Arg 340	Ser	Ser	Asp	His	Arg 345	Gln		Asn	Ser	Leu 350	Met	Gln
Thr	Glu	G1u 355	Cys	Pro	Pro	Met	Leu 360	Asp	Ala	Thr	Xaa	G1n 365	Gln	Gln	Gln
Gln	Va1 370	Ala	Ala	Cys	Glu	G1y 375	Arg	Ala	Phe	Asp	Asn 380	Glu	Gln	Asp	Gly
Va1 385	Thr	Tyr	Ser	Tyr	Ser 390	Phe	Phe	His	Phe	Cys 395	Leu	Val	Leu	Ala	Ser 400
Leu	His	Val	Met	Met 405	Thr	Leu	Thr	Asn	Trp 410	Tyr	Lys	Pro	Gly	Glu 415	Thr
Arg	Lys	Met	Ile 420	Ser	Thr	Trp	Thr	A1a 425	Val	Trp	Val	Lys	Ile 430	Cys	Ala
Ser	Trp	A1a 435	Gly	Leu	Leu	Leu	Tyr 440	Leu	Trp	Thr	Leu	Va1 445	Ala	Pro	Leu
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					aaa Lys					288
					agt Ser					336
					gat Asp					384
					gca Ala					432

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			-		-	-		acc Thr		-	_			_		528
-						-	-	gaa Glu 185				-		_	-	576
							-	ata Ile			-	-	_	-	•	624
							-	cag G1n	-	-		-	-			672
								caa Gln	_			-				720
		-		-	-			tta Leu		-	-			•		768
Phe	Asp	Val	Tyr	Ala	Пe	Lys	Pro	ggt Gly 265	His		-			Āsp		816
								gtt Val	_	-			_			864
	-			_			_	gag Glu		-	-	_				912
								aca Thr								960

305					310				315					320	
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			-	-			_			-	_	aaa Lys 350	-	-	1056
			_						-	-	-	gat Asp			1104
_	_	_			_	-		-	-			999 Gly			1152
			_	_		_			_	_		aaa Lys			1200
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He	Ser	Ala	Ala		Glu	Lys	Ala	He	-	Lys	Phe	Gly	Gly	He	Asp
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He	Leu	Val		Asn	Ala	Ser	Ala		Ser	Leu	Thr	Asn		Leu	Asp
T 1		T .	100					105					110		
		115				·	Leu 120					125			·
Thr	Tyr 130	Leu	Ala	Ser	Lys	Ala 135	Cys	He	Pro	Tyr	Leu 140	Lys	Lys	Ser	Lys
	Ala	His	He	Leu		He	Ser	Pro	Pro	Leu	Asn	Leu	Asn	Pro	Val
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				165			Tyr		170					175	
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Asn	Ala	Leu 195	Trp	Pro	Lys	Thr	Ala 200	Пe	His	Thr	Ala	Ala 205	Met	Asp	Met
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Ala 225	Asp	Ala	Ala	Tyr	Ser 230	He	Phe	Gln	Lys	Pro 235		Ser	Phe	Thr	G1y 240
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Phe	Asp	Val	Tyr 260	Ala	Пе	Lys	Pro	G1y 265	His	Pro	Leu	Gln	Pro 270		Phe
Phe	Leu	Asp 275	Glu	Tyr	Pro	Glu	A1a 280	Val	Ser	Lys	Lys	Va1 285		Ser	Thr
Gly	A1a 290	Val	Pro	Glu	Phe	Lys 295	Glu	Glu	Lys	Leu	G1n 300		Gln	Pro	Lys
Pro 305	Arg	Ser	Gly	Ala	Val 310	Glu	Glu	Thr	Phe	Arg 315		Val	Lys	Asp	Ser 320
	Ser	Asp	Asp	Va1 325		Lys	Ala	Thr	G1n 330		Ile	Tyr	Leu	Phe 335	
Leu	Seŗ	Gly	G1u 340		Gly	Gly	Thr	Trp 345		Leu	Asp	Leu	Lys 350		Lys
Gly	Gly	Asn 355		Gly	Tyr	Gly	G1u 360		Ser	Asp	Gln	A1a 365		Val	۷al
Met	Ser 370		Thr	Thr	Asp	Asp 375	Phe	Val	Lys	Met	Phe 380		Gly	Lys	Leu
Lys		Thr	Met	Ala	Phe		Ser	Glv	Lvs	Leu		Πe	lvs	Glv	Asn
385		• •		. =/	390			- · J	_,, 5	395	_, 5		-,, -	,	400
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66

	115					120				125				
			tta Leu	-	-							-		432
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			gaa Glu 165											528
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Arg	Gln	Lys	Asp	Val	Lys	He	Val		Val	Glu	Lys	Lys		Asn	Glu	
		115			•		120				•	125				
He	Leu 130	Asn	Arg	Leu	Glu	Lys 135	Thr	Lys	Val	Glu	Arg 140	Phe	Pro	Asp	Leu	
A1a 145	Ala	Glu	Lys	Glu	Cys 150	Arg	Asp	Arg	Glu	Glu 155	Arg	Asn	Glu	Lys	Lys 160	
Ala	Gln	He	Gln	Glu 165	Met	Lys	Lys	Arg	Glu 170	Lys	Glu	Glu	Met	Lys 175	Lys	
Lys	Arg	Glu	Met 180	Asp	Glu	Leu	Arg	Ser 185	Tyr	Ser	Ser	Leu	Met 190	L y s	Val	
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Leu	Cys	Ala	Gly	Gly	Gly	Gly	Leu	•	Gly	Pro	Val	Val	_	Thr	Ala	•
			20					25					30			
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ata	220	220	gac	220	ata	ata	ata	++~	ctc	220	acc	200	000	a 20	C20	192
			Asp													132

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Gly	Ser	A1a 35		Gly	Gly	Gly	G1y 40		Ala	Xaa	Xaa	Leu 45	30 Asp	Ala	Leu	

Val	Lys 50	Lys	Asp	Lys	Val	Val 55	Val	Phe	Leu	Lys	Gly 60	Thr	Pro	Glu	Gln	
Pro 65	Gln	Cys	Gly	Phe	Ser 70	Asn	Ala	Val	Val	G1n 75	Ile	Leu	Arg	Leu	His 80	
Gly	Val	Arg	Asp	Tyr 85	Ala	Ala	Tyr	Asn	Va1 90	Leu	Asp	Asp	Pro	Glu 95		
Arg	Gln	Gly	Ile 100	Lys	Asp	Tyr	Ser	Asn 105	Trp	Pro	Thr	Пe	Pro 110		Val	
Tyr	Leu	Asn 115		Glu	Phe	Val	Gly 120		Cys	Asp	He	Leu 125		Gln	Met	
His	Gln 130		Gly	Asp	Leu	Val 135	Glu	Glu	Leu	Lys	Lys 140		Gly	Ile	His	
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	gcg Ala			tgc Cvs												96
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		-	20 cgc	gag Glu	ctc	999	ata	25 cgc	tct	tcg	aag	tcc	30 gca	ggt	gcc	144
Arg	Gly	Asp 35 gaa	cgc Arg	gag	ctc Leu tca	999 Gly gag	ata Ile 40 ggt	25 cgc Arg	tct Ser ttg	tcg Ser tgc	aag Lys ggg	tcc Ser 45	30 gca Ala tcg	ggt Gly gcc	gcc Ala	1 <u>44</u>

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			-		_	-		ggt Gly		_		576
								aac Asn 205				624
								aca Thr				672
								caa G1n				720
								gaa Glu				768

	gcc Ala															816
	aag Lys					-			-			_			•	864
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	ggt Gly											_	_	-		960
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Pro 65	Gln	Thr	Gly	Gly	Thr 70		Glu	Ser	Gln	Trp 75		Lys	Thr	Ser	G1n 80	
Pro	Glu	Asp	Leu	Thr 85	Asp	Gly	Ser	Tyr	Asp 90	Asp	Val	Leu	Asn	Ala 95		

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He	Ile	G1u 115		Ala	Leu	He	Thr 120	Leu	Gly	Asn	Asn	Ala 125	Ala	Phe	Ser
Val	Asn 130	Gln	Ala	Ile	Ile	Arg 135	Glu	Leu	Gly	Gly	Ile 140	Pro	Ile	Val	Ala
Asn 145	Lys	He	Asn	His	Ser 150	Asn	Gln	Ser	Пe	Lys 155	Glu	Lys	Ala	Leu	Asn 160
Ala	Leu	Asn	Asn	Leu 165	Ser	Val	Asn	Val	Glu 170	Asn	Gln	He	Lys	I 1e 175	Lys
			180					185				_	190	Leu	
		195					200					205		Thr	
	210					215					220		•	Leu	
225					230					235				Leu	240
				245					250				•	Leu 255	
			260					265					270	His	
		275					280		-			285		He	•
	290					295					300			Phe	
305					310				-	315				Gln Lys	320
	Thr			325			піз	ASP	330	GIU	Vai	L y S	GIU	335	VdI
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		tta Leu						-				-		_		192
		gac Asp														240
		tcc Ser														288
		aag Lys														336
		atc Ile 115	Ser	Ser	Āla	Pro	Phe	Leu	Leu		Gln		Leu			384
		atc Ile														432
		gga G1y														480
gaa	tat	aag	ссс	ctt	tcg	ggc	att	cgg	tac	atg	tgg	tcg	tac	cat	tta	528

Glu	Tyr	Lys	Pro	Leu 165	Ser	Gly	Ile	Arg	Tyr 170	Met	Trp	Ser	Tyr	His 175	Leu	
						_					gcg Ala	_	•		_	576
						_		-			aac Asn	_	-			624
											tcc Ser 220					672
											tta Leu			~ ~		720
			-				_		-		aac Asn	•	_		_	768
											tgc Cys					816
											aac Asn	_		_		864
											aca Thr 300					912
											ttt Phe					960
											gtg Val				_	1008
ttc	act	gtt	ttt	gga	gga	ctc	atg	gct	ttt	aac	tac	aat	cgg	gca	ttc	1056

Phe Thr Val Phe			Ala Phe 345	Asn Tyr	Asn Ar 35	-	Phe
cag gtg tgg gca Gln Val Trp Ala 355							
gta gcc cat agt Val Ala His Ser 370	r Phe Leu S				Leu As		
ttc ctg tgt ttt Phe Leu Cys Phe 385							
aag ccc tac ttt Lys Pro Tyr Phe							
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Leu Ser Leu Ala 20	Met Met P		Phe Arg 25	Phe Ile	Thr Thi	Leu	Leu
Val His Ile Phe							

		35					40					45			
Gly	Va1 50	Leu	Trp	Trp	Leu	Tyr 55	Tyr	Asp	Tyr	Thr	Asn 60	Asp	Leu	Ser	Пe
G1u 65	Leu	Asp	Thr	Glu	Arg 70	Glu	Asn	Met	Lys	Cys 75	Val	Leu	Gly	Phe	A1a 80
Ile	Val	Ser	Thr	G1y 85	He	Thr	Ala	Val	Leu 90	Leu	Val	Leu	Ile	Phe 95	Val
Leu	Arg	Lys	Arg 100	Ile	Lys	Leu	Thr	Val 105	Glu	Leu	Phe	Gln	Ile 110	Thr	Asn
Lys	Ala	I le 115	Ser	Ser	Ala	Pro	Phe 120	Leu	Leu	Phe	Gln	Pro 125		Trp	Thr
	130					135				Trp	140				
145					150					Met 155					160
				165					170	Met				175	
			180					185		Leu			190		
Thr	He	Ala 195	Gly	Ala	Val	Xaa	Thr 200	Cys	Tyr	Phe	Asn	Arg 205	Ser	Lys	Asn
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225					230					Phe 235					240
				245					250	Gln				255	
Gln	His	Gly	A1 a 260	Leu	Ser	Arg	Tyr	Leu 265	Phe	Arg	Cys	Cys	Tyr 270	Cys	Cys
		275					280			Leu		285			
Thr	Thr 290	Thr			Asn			Asp	Phe	Cys	Thr 300	Ser	Ala	Lys	Asp
305					310					His 315					320
Cys	Phe	Gly	Asp	Phe 325	He	He	Phe	Leu	Gly 330	Lys	Val	Leu	Val	Va1 335	Cys
Phe	Thr	Val	Phe 340	Gly	Gly	Leu	Met	A1a 345	Phe	Asn	Tyr	Asn	Arg 350	Ala	Phe
Gln	Val	Trp 355	Ala	Val	Pro	Leu	Leu 360	Leu	Val	Ala	Phe	Phe 365	Ala	Tyr	Leu
Val	A1a 370	His	Ser	Phe	Leu	Ser 375	Val	Phe	Glu	Thr	Val 380	Leu	Asp	Ala	Leu
Phe	Leu	Cys	Phe	Ala	Val	Asp	Leu	Glu	Thr	Asn	Asp	Gly	Ser	Ser	Glu

385	•	_			390					395					400	
Lys	Pro	Tyr	Phe	Met 405	Asp	GIn	Glu	Phe	Leu 410	Ser	Phe	Val	Lys	Arg 415	Ser	
Asn	Lys	Leu	Asn 420	Asn	Ala	Arg	Ala	G1n 425	Gln	Asp	Lys	His	Ser 430	Leu	Arg	
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					ttg Leu											. 48
gga Gly	gtg Val	tac Tyr	aag Lys 20	tcc Ser	gcg Ala	gag G1u	cag G1n	999 G1y 25	gag Glu	gtg Val	gaa G1u	aac Asn	gga Gly 30	cga Arg	tgt Cys	96
					aac Asn											144
gaa Glu	agg Arg 50	ttt Phe	aca Thr	aaa Lys	gat Asp	act Thr 55	gca Ala	agg Arg	ttc Phe	aag Lys	gat Asp 60	gag G1u	tta Leu	gat Asp	atc Ile	192
					aaa Lys 70											240
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10

15

1

	-	-	atg Met		-		_			96
			gaa Glu							144
	-		gaa Glu 55			 _		_		192
			gtg Val			-	-	_	•	240
			gcc Ala							288
			acc Thr							336
			tgt Cys							384
			999 Gly 135							432
			ctt Leu							480
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<220>

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aag ttc aag ctt ttt acc ttg gtg tct gcc tgt atc cca gtg ttc agg
Lys Phe Lys Leu Phe Thr Leu Val Ser Ala Cys Ile Pro Val Phe Arg
20 25 30

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		aag Lys						-				_	144
		aga Arg						-				-	192
		gag Glu 70						_	_	-	-		240
		ttc Phe		-	_	-		-	-			_	288
		gac Asp											336
-		gtt Val	-		_	_	_	-	-		-		384
		ctg Leu											432
		gca Ala 150											480
		tgg Trp								-			528
		ctg Leu											576
		tcc Ser				-					-		624

								cac His 220		-	_	_	67	2
								att Ile	_		-	-	72	0
						-	-	aat Asn	_				76	8
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<212> PRT

<213> Homo sapiens

<400> 52

 Met
 Pro
 Leu
 Leu
 Lys
 Leu
 Val
 His
 Gly
 Ser
 Pro
 Leu
 Val
 Phe
 Gly
 Gly</th

105

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	ctc Leu										192
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	tcc Ser										288
	gtg Val 100										336
	ctc Leu										384
	aaa Lys			-			_		_		432
	cgg Arg										480
	gag Glu				_	_		-	 -	-	528
	aaa Lys 180										576

										ggg Gly		624
_										atg Met	_	672
										tac Tyr	cac His 240	720
										aac Asn 255		768
										ccc Pro		816
			_	-	-			•	 	ctt Leu	•	864
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										att Ile		960
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48
96
144
192
195

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<213> Homo sapiens

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Glu	Arg	Arg 35	Lys	Lys	Glu	Ala	Asn 40	Lys	Ala	Thr	Arg	Ala 45	Asn	His	Asn	
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														gtt Val		96
														gca Ala		144
								-	_	-		_	_	atg Met	_	192
														gtg Val		240
														ttt Phe 95		288

tgg Trp												336
cta Leu				_			-	-	-	_		384
cga Arg 130										 _	-	432
aag Lys												480
ggc Gly		-	-	-								528
aag Lys			-	-	_	_	-					576
tat Tyr												624
gca Ala 210												672
cct Pro												720
atc Ile												768
ctg Leu												816

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tag *									1011

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48

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Phe Arg Ala Thr Arg Lys Pro Leu Val Gln Thr Thr Pro Arg Leu Val
Tyr Lys Trp Phe Leu Leu Ile Tyr Lys Ile Ser Tyr Ala Thr Gly Ile
                    150
                                        155
Val Gly Tyr Met Ala Val Met Phe Thr Leu Phe Gly Leu Asn Leu Leu
                                    170
Phe Lys Ile Lys Pro Glu Asp Ala Met Asp Phe Gly Ile Ser Leu Leu
                                185
Phe Tyr Gly Leu Tyr Tyr Gly Val Leu Glu Arg Asp Phe Ala Glu Met
                            200
                                                205
Cys Ala Asp Tyr Met Ala Ser Thr Ile Gly Phe Tyr Ser Glu Ser Gly
                        215
Met Pro Thr Lys His Leu Ser Asp Ser Val Cys Ala Val Cys Gly Gln
                    230
                                        235
Gln Ile Phe Val Asp Val Ser Glu Glu Gly Ile Ile Glu Asn Thr Tyr
                245
                                    250
Arg Leu Ser Cys Asn His Val Phe His Glu Phe Cys Ile Arg Gly Trp
            260
                                265
Cys Ile Val Gly Lys Lys Gln Thr Cys Pro Tyr Cys Lys Glu Lys Val
                            280
Asp Leu Lys Arg Met Phe Ser Asn Pro Trp Glu Arg Pro His Val Met
                        295
                                            300
Tyr Gly Gln Leu Leu Asp Trp Leu Arg Tyr Leu Val Ala Trp Gln Pro
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Val Ile Ile Gly Val Val Gln Gly Ile Asn Tyr Ile Leu Gly Leu Glu
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			cct Pro												240
			gcc Ala	-	_	_	 -	-	•	•	•	-			288
			tac Tyr 100												336
			aac Asn												384
ctc Leu	agc Ser 130	tag *													393
	_^	2105	60												
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		35					40					45					
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			_	ctg Leu				-	-				-	-		24	0
				ggc Gly 85												. 28	8
		-		tgt Cys		-	_		_		_					33	6
•	•	•		ccc Pro	_				_		~			~	•	38	4
				ttc Phe	_			_				-	_			43	2
		-		ttg Leu			-		_						-		0
	-			ttt Phe 165	Val			Ala		Gly						52	:8
				ctt Leu				-				-			-	. 57	6
	_		Val	gag G1u	_	-	-	-	-							62	4
				gaa Glu	-	-		_	_			_				67	2

210		•			215					220					
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												gtg Val		-	768
-			-			-	_					cat His 270		-	816
_	_		_			_	-					cca Pro	_		864
												acg Thr		-	912
												gat Asp			960
						-				_		ctc Leu	_		1008
				_								gga Gly 350	_		1056
				_		-	-		-		_	ttg Leu			1104
								-			-	ttt Phe			1152
												ctt Leu			1200

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96

385 390 395 400 ggc atg ttc ctc tat att tct ctg gca gat atg ttt cca gag atg aat 1248 Gly Met Phe Leu Tyr Ile Ser Leu Ala Asp Met Phe Pro Glu Met Asn 405 410 415 gat atg ctg aga gaa aag gta act gga aga aaa acc gat ttc acc ttc 1296 Asp Met Leu Arg Glu Lys Val Thr Gly Arg Lys Thr Asp Phe Thr Phe 420 425 430 ttc atg att cag aat gct gga atg tta act gga ttc aca gcc att cta 1344 Phe Met Ile Gln Asn Ala Gly Met Leu Thr Gly Phe Thr Ala Ile Leu 435 440 445 ctc att acc ttg tat gca gga gaa atc gaa ttg gag taa 1383 Leu Ile Thr Leu Tyr Ala Gly Glu Ile Glu Leu Glu * 450 455 460 <210> 62 <211> 460 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(460) <223> Xaa = Any Amino Acid <400> 62 Met Ala Pro Gly Arg Ala Val Ala Gly Leu Leu Leu Leu Ala Ala Ala 10 Xaa Leu Gly Gly Val Ala Glu Gly Pro Gly Leu Ala Phe Ser Glu Asp Val Leu Ser Val Phe Gly Ala Asn Leu Ser Leu Ser Ala Ala Gln Leu Gln His Leu Leu Glu Gln Met Gly Ala Ala Ser Arg Val Gly Val Pro 55 60 Glu Pro Gly Gln Leu His Phe Asn Gln Cys Leu Thr Ala Glu Glu Ile 70 75 Phe Ser Leu His Gly Phe Ser Asn Ala Thr Gln Ile Thr Ser Ser Lys 90 Phe Ser Val Ile Cys Pro Ala Val Leu Gln Gln Leu Asn Phe His Pro 105 110

Cys	Glu	Asp 115	Arg	Pro	Lys	His	Lys 120	lhr	Arg	Pro	Ser	His 125	Ser	Glu	Val
Trp	Gly 130	Tyr	Gly	Phe	Leu	Ser 135	Val	Thr	He	He	Asn 140	Leu	Ala	Ser	Leu
Leu 145	Gly	Leu	He	Leu	Thr 150	Pro	Leu	He	Lys	Lys 155	Ser	Tyr	Phe	Pro	Lys 160
He	Leu	Thr	Phe	Phe 165	۷a٦	Gly	Leu	Ala	Ile 170		Thr		Phe	Ser 175	Asn
Ala	He	Phe	Gln 180	Leu	He	Pro	Glu	Ala 185	Phe	Gly	Phe	Asp	Pro 190	Lys	Val
Asp	Ser	Tyr 195	Val	Glu	Lys	Ala	Va1 200	Ala	Val	Phe	Gly	Gly 205	Phe	Tyr	Leu
Leu	Phe 210	Phe	Phe	Glu		Met 215	Leu	Lys	Met	Leu	Leu 220	Lys	Thr	Tyr	Gly
225	Asn				230					235					240
	Thr			245					250					255	
	Ala		260					265					270		
Asn	Val	Ser 275	Val	Val	Ser	Leu	G1n 280	Asp	Gly	Lys	Lys	G1u 285	Pro	Ser	Ser
Cys	Thr 290	Cys	Leu	Lys	Gly	Pro 295	Lys	Leu	Ser	Glu	11e 300	Gly	Thr	He	Ala
Trp 305	Met	He	Thr	Leu	Cys 310	Asp	Ala	Leu	His	Asn 315	Phe	Пe	Asp	Gly	Leu 320
	Ile			325					330			•		335	
	He		340					345					350	•	
	Пe	355					360					365			
	Phe 370					375					380				
385	Val				390					395					400
Gly	Met	Phe	Leu	Tyr 405	He	Ser	Leu	Ala	Asp 410	Met	Phe	Pro	Glu	Met 415	Asn
Asp	Met	Leu	Arg 420	Glu	Lys	Val	Thr	G1y 425	Arg	Lys	Thr	Asp	Phe 430	Thr	Phe
Phe	Met	I le 435	Gln	Asn	Ala	Gly	Met 440	Leu	Thr	Gly	Phe	Thr 445	Ala	Пе	Leu
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	ctc Leu													96
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	cag G1n													192
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						cat His 60					192
						gac Asp			-		240
						tca Ser	-	-	_	_	288
						aca Thr					336
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Ser	Leu 50	Gln	Vaì	Pro	Arg	Pro 55	Ser	Pro	Gly	His	His 60	His	Pro	Pro	Ala	
Va1 65	Lys	Glu	Met	Lys	G1u 70		Gln	Thr	Glu	Arg 75		Ile	Pro	Met	Ser 80	
Asp	Ser	Leu	Tyr	Arg 85	His	Asp	Ser	Asp	Thr 90		Ser	Asp	Ser	Leu 95		
Ser	Ser	Cys	Ser 100	Ser	Pro	Pro	Ala	Cys 105	Gln	Ala	Thr	Glu	Asp 110	Val	Asp	
Tyr	Thr	Gln 115	Val	Val	Phe	Ser	Asp 120	Pro	Gly	Glu	Leu	Lys 125	Asn	Asp	Ser	
Pro	Leu 130	Asp	Tyr	Glu	Asn	I le 135	Lys	Glu	Ile	Thr	Asp 140	Tyr	Val	Asn	Val	
Asn 145	Pro	Glu	Arg	His	Lys 150	Pro	Ser	Phe	Trp	Tyr 155	Phe	Val	Asn	Pro	Ala 160	
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	gcc Ala															96
gcc Ala	cag Gln	gcc Ala 35	cgg Arg	cga Arg	ctc Leu	cag G1n	99a G1y 40	gac Asp	gtg Val	gca Ala	ggc Gly	gcc Ala 45	ctg Leu	gag G1u	gat Asp	144
	gaa Glu 50															192

	agc Ser				-	-					_	_		-	•	240
	gac Asp	_	-		-		-			-		_		_		288
	gcg Ala		-	_	_							-		-	-	336
	cgc Arg															384
_	cgc Arg 130	tga *														393
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Gln	Ala	He	Cvs	Lou	1	_			10					15		
			20	Leu	Leu	Pro	Glu	Arg 25		Ser	Ala	Tyr	Asn 30		Arg	
Ala	Gln	A1a 35	20					25	Āla			-	30	Asn	•	
	Gln Glu 50	35	20 Arg	Arg	Leu	Gln	Gly 40	25 Asp	Ala Val	Ala	Gly	A1a 45	30 Leu	Asn Glu	Asp	
Leu	Glu	35 Arg	20 Arg Ala	Arg Val	Leu Glu	Gln Leu 55	Gly 40 Ser	25 Asp Gly	Ala Val Gly	Ala Arg	Gly Gly 60	Ala 45 Arg	30 Leu Ala	Asn Glu Ala	Asp Arg	
Leu Gln 65	Glu 50	35 Arg Phe	20 Arg Ala Val	Arg Val Gln	Leu Glu Arg 70	Gln Leu 55 Gly	Gly 40 Ser Leu	25 Asp Gly Leu	Ala Val Gly Ala	Ala Arg Arg 75	Gly Gly 60 Leu	Ala 45 Arg Gln	30 Leu Ala Gly	Asn Glu Ala Arg	Asp Arg Asp 80	
Leu Gln 65 Asp	Glu 50 Ser	35 Arg Phe Ala	20 Arg Ala Val Arg	Arg Val Gln Arg 85	Leu Glu Arg 70 Asp	Gln Leu 55 Gly Phe	Gly 40 Ser Leu Glu	25 Asp Gly Leu Arg	Ala Val Gly Ala Ala 90	Ala Arg Arg 75 Ala	Gly Gly 60 Leu Arg	Ala 45 Arg Gln Leu	30 Leu Ala Gly Gly	Asn Glu Ala Arg Ser 95	Asp Arg Asp 80 Pro	

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					tgc Cys		-	-	-			_	192
					ggc Gly 70								240
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Lys	Val	Va1 35	Ser	Gly	Arg	He	11e 40	Asn	Gly	Tyr	Cys	Arg 45	Gly	Asp	Trp	
				gtg Val												192
				gtg Val												240
				gtc Val 85												288
				gcc Ala												336
				ctg Leu												384
				gcc Ala												432
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aca Thr	gac Asp	ccc Pro	agc Ser	caa Gln 165	gcc Ala	cag G1n	gtg Val	cca Pro	gta Val 170	999 G1y	ctg Leu	gac Asp	cag Gln	tct Ser 175	gaa G1u	528
				cct Pro												576
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	gat Asp		_					_			-			240 [°]
	tgc Cys													288
	tca Ser	_		_			_	_		_		_	-	336
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Phe Gly Leu Asp Gly Tyr Arg Gly Tyr Ser Leu Ala Asp Trp Val Cys
Leu Ala Tyr Phe Thr Ser Gly Phe Asn Ala Ala Ala Leu Asp Tyr Glu
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Ala Asp Gly Ser Thr Asn Asn Gly Ile Phe Gln Ile Asn Ser Arg Arg
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Trp Cys Ser Asn Leu Thr Pro Asn Val Pro Asn Val Cys Arg Met Tyr
Cys Ser Asp Leu Leu Asn Pro Asn Leu Lys Asp Thr Val Ile Cys Ala
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Met Lys Ile Thr Gln Glu Pro Gln Gly Leu Gly Tyr Trp Glu Ala Trp
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Arg His His Cys Gln Gly Lys Asp Leu Thr Glu Trp Val Asp Gly Cys
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Asp Phe
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			gag Glu													192	2
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			acc Thr										-			288	3
			gga Gly 100													336	5
	cag Gln	tga *														345	5
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	Trp	Ser	Ser 20		Ala	Phe	He	11e 25		Tyr	Val	Val	Ala 30		Leu		
Ser	Gly	His 35	Val	Asn	Pro	Phe	Leu 40		Tyr	Пe	Ser	Asp 45		Gly	Thr		
	50		Glu			55					60						
Phe 65	Leu	Gly	Ala	Ala	Thr 70	Met	Tyr	Thr	Arg	Tyr 75	Lys	He	Val	Gln	Lys 80		

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999 Gly 130									432
aat Asn									480
aca Thr				-	_		-	 	528
gac Asp									576
atg Met									624
ttc Phe 210									672
ctt Leu								gaa Glu 240	720
atg Met									768
gag G1u									816
gtg Val									864

			acc Thr													g	912
			gaa Glu													g	960
_	ctg Leu	_	taa *													Ğ	972
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			20					25					30				
Leu	Ala	Arg 35	Arg	Arg	Lys	Lys	11e 40	Leu	Phe	Tyr	Cys	His 45	Phe	Pro	Asp		
Leu	Leu 50	Leu	Thr	Lys	Arg	Asp 55	Ser	Phe	Leu	Lys	Arg 60	Leu	Tyr	Arg	Ala		
Pro 65	Ile	Asp	Trp	Пе	G1u 70	Glu	Tyr	Thr	Thr	G1y 75	Met	Ala	Asp	Cys	Ile 80		
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Ser	Leu	Ser	His 100		Asp	Pro	Asp	Val 105		Tyr	Pro	Ser	Leu 110		Val		
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			20				25					30			
				cgc Arg								-		-	144
				cag G1n									-	_	192
				ctc Leu	-		_	_	-		-	_	-	-	240
				ttc Phe 85		-	-		_	-				_	288
-	-	-		aat Asn	_				_	•			_	_	336
				ttt Phe								_			384
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Asp Val Leu Ile Asn Asn Ala Gly Ile Phe Gln Cys Pro Tyr Met Lys
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Thr Glu Asp Gly Phe Glu Met Gln Phe Gly Val Asn His Leu Gly His
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144		gtg Val		-	_											
192	•	cag G1n	-		_						-			-		-
240	•	gtg Val			-						_	-			_	-
288	_	ggc Gly 95		-						_				_		-
336		gtg Val														
384	-	gaa Glu	_	-												
432	-	cca Pro				-				-	-	-	_			_
480		agc Ser														
528		aat Asn 175						-								
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Se	r Lei	ı Ser	Asn 180	Gly	Thr	Ser	Asp	Ala 185	Asp	Leu	Phe	Asp	Ser 190	His	Asp	
	c aga p Arg	-	Asp											•	•	624
	t ato 1 110 210	e Met			-	_	_	-	-			-	_			672
	g gta s Va 5															720
	g ta t Tyi															768
	c caq p Gli															816
	c tca u Sei										-	_		_		864
	c aat r Ası 290) Pro														912
	t gat n Asp 5		-				_		-		-	-		•		960
	g gti p Va															1008
	t cca s Pro															1056
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_	_													tct Ser		1200
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			-	_		_			-					cca Pro		1344
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200

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Phe	Val	Pro	Trp	Cys ยร	Lys	Lys	Ser	Leu	Val on	Val	Ser	Ser	Arg	Lys os			

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	Leu		Ala					Pro								
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Phe	Ala		Pro	Phe	Thr	Asn		Arg	Lys	Ala	Tyr		Glu	Arg	Arg	
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Pro Glu Arg Trp Gly Pro Gly Arg Phe Asp Tyr Trp Gly Asn Ser His
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Gln Ile Met His Leu Leu Ser Val Gly Ser Ile Leu Gln Leu His Ala
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Arg His Ser Leu Leu Ser Pro Leu Leu Ser Val Thr Ser Phe Arg Arg
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ttc tac aga ggt gac agc cca aca gat tcc caa aag gac atg att gaa
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Phe Tyr Arg Gly Asp Ser Pro Thr Asp Ser Gln Lys Asp Met Ile Glu
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Lys 145	Asn	Lys	Asn	Lys	Glu 150	Gln	Arg	Leu	Arg	Ala 155	Pro	Asp	Leu	Glu	Tyr 160	
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														gtt Val		144
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														gtg Val 95	-	288
							_	_		_				cct Pro		336

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11e 65	Phe	His	leu	Leu	Pro	Thr	Tyr	Phe	Val	Asp	Thr	Ala	He	Tyr	Ser	
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Asp	Ile				70					75					80	
		Ser	Gly	G1y 85	70 Gly	His	Pro	Tyr	Leu 90	75 Thr	Gly	Leu	Ala	Va1 95	80 Ala	
Gly	Ile	Ser Ala	Gly Tyr 100	Gly 85 Tyr	70 Gly Leu	His Gly	Pro Leu	Tyr Glu 105	Leu 90 Gly	75 Thr Ala	Gly Ile	Leu Ile	Ala Gly 110	Val 95 Pro	80 Ala Ile	
Gly Leu	Ile Gly	Ser Ala Cys 115	Gly Tyr 100 Ile	Gly 85 Tyr Leu	70 Gly Leu Val	His Gly Val	Pro Leu Ala 120	Tyr Glu 105 Ser	Leu 90 Gly Asn	75 Thr Ala Ile	Gly Ile Tyr	Leu Ile Ser 125	Ala Gly 110 Ala	Val 95 Pro Met	80 Ala Ile Leu	

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138

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	100			105			110		
						ctg Leu			384
						ggc Gly 140			432
						tcc Ser			480
						cag Gln			528
						gtg Val			576
		-	-		_	gcc Ala			624
						gag Glu 220			672
						ctg Leu			720
						ggt Gly			768
						atc Ile			816
				-		gag Glu	_	~ ~	864

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150

165

141

450 455 460 ccc ctc acc att tca gga aag atc cag aaa ttc aaa ctt cga gag cag 1440 Pro Leu Thr Ile Ser Gly Lys Ile Gln Lys Phe Lys Leu Arg Glu Gln 465 470 475 480 atg gaa cga cat cta aat ctg tga 1464 Met Glu Arg His Leu Asn Leu * 485 <210> 100 <211> 487 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(487) <223> Xaa = Any Amino Acid <400> 100 Met Trp Gly Pro Asn Ser Tyr Ala Trp Val Leu Met Gln Leu Ala Thr Ala Gln Ala Gly Ile Ile Leu Val Ser Val Asn Pro Ala Tyr Gln Ala Met Glu Leu Glu Tyr Val Leu Lys Lys Val Gly Cys Lys Ala Leu Val 40 Phe Pro Lys Gln Phe Lys Thr Gln Gln Tyr Tyr Asn Val Leu Lys Gln 55 Ile Cys Pro Glu Val Glu Asn Ala Gln Pro Gly Ala Leu Lys Ser Gln Arg Leu Pro Asp Leu Thr Thr Val Ile Ser Val Asp Ala Pro Leu Pro 90 Gly Thr Leu Leu Leu Asp Glu Val Val Ala Ala Gly Ser Thr Arg Gln 105 His Leu Asp Gln Leu Gln Tyr Asn Gln Gln Phe Leu Ser Cys His Asp 120 Pro Ile Asn Ile Gln Phe Thr Ser Gly Thr Thr Gly Ser Pro Lys Gly 135 140 Ala Thr Leu Ser His Tyr Asn Ile Val Asn Asn Ser Asn Ile Leu Gly

155

175

170

Glu Arg Leu Lys Leu His Glu Lys Thr Pro Glu Gln Leu Arg Met Ile

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Met	Cys	Leu 195	Met	Tyr	Gly	Ala	Thr 200	Leu	He	Leu	Ala	Ser 205	Pro	He	Phe
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			420					425					Leu 430		·
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He	Ser 450	His	Phe	Lys	He	Pro 455	Lys	Tyr	He	Val	Phe 460	Val	Thr	Asn	Tyr
Pro 465	Leu	Thr	He	Ser	Gly 470	Lys	He	Gln	Lys	Phe 475	Lys	Leu	Arg	Glu	G1n 480
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Pro	Trp 50	Ala	Leu	Gln	Thr	Leu 55	Ala	Val	Asp	Tyr	Gly 60	Ser	Tyr	He	Arg		
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Val	Phe	Val	Thr	Va1 85	Phe	Gly	Val	His	Leu 90	Asn	Lys	Trp	Gln	Leu 95	Asp		
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arg	ыу	ыу		Arg	rne	Leu	Ala		Ser	He	Ala	Ser		Asp	Asp		
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qac	agc	ctc	ttc	atc	tat	qac	tac	aat	act.	gca	ดลล	ลลด	ลลด	tca	caa	144	
Asp	Ser	Leu	Phe	Ιlė	Tyr	Asp	Cys	Ser	Ala	Ala	Glu	Lys	Lys	Ser	Gln	1.,	
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~ ~ ~		222	900							_						100	
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uiu	50	Lys	uly	Glu	vəh	55	710	Leu	ush	וונט	60	261.	чіу	Ald	116		
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													_	gcg Ala 175		528
														gtg Val		576
cgt Arg	atc Ile	tcc Ser 195	gtg Val	gtg Val	cca Pro	act Thr	cag Gln 200	ccc Pro	999 Gly	ctg Leu	ctt Leu	ctg Leu 205	tcc Ser	tcc Ser	tct Ser	624
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														cag Gln		720

cag Gln										768
gtg Val										816
gac Asp										864
cac His 290					-				-	 912
ctc Leu										960
gac Asp										1008
ggt Gly					_				_	 1056
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	Asp	Gln	Trp	G1n 325		Val	Pro	Glu	Ser 330		Val	Leu	Lys	Lys 335		
Ser	Gly	Val	Leu 340		Gly	Asn	Trp	Ala 345	Met	Leu	Glu	Gly	Ser 350		Gly	
Ala	Asp	A1a 355		Phe	Ser	Ser	Leu 360		Lys	Ala	Thr	Phe 365		Asn	Val	
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Lys 385		Gln	Arg	Arg	Arg 390		Pro	Pro	Pro	G1y 395		Asp	Gly	His	Ala 400	٠.
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	-					gaa Glu						-	_		gga Gly	336
						gat Asp					_	-			_	384
						ttt Phe 135	-		-		-	_				432
						aga Arg			_	-		-	_			480
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 Thr
 Ile
 Leu
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 Gln
 Ala
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His	Glu	Asn 35	Lys	Tyr	Gly	Lys	Gly 40	He	Tyr	Phe	Ala	Lys 45	Asp	Ala	Ile	
Tyr	Ser 50	His	Lys	Asn	Cys	Pro 55	Tyr	Asp	Ala	Lys	Asn 60	Val	Val	Met	Phe	
Va1 65	Ala	Gln	Val	Leu	Va1 70	Gly	Lys	Phe	Thr	Glu 75	Gly	Asn	Ile	Thr	Tyr 80	
Thr	Ser	Pro	Pro	Pro 85	Gln	Phe	Asp	Ser	Cys 90	Val	Asp	Thr	Arg	Ser 95	Asn	
Pro	Ser	Val	Phe 100	Va1	He	Phe	Gln	Lys 105	Asp	Gln	Val	Tyr	Pro 110	Gln	Tyr	
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			ctc Leu 20													96
			ctc Leu													144
			aga Arg													192

		-	-	-	_				-		-	_	ggc Gly		240
			-								-		gtg Val 95		288
-	_						_				_	-	agc Ser	-	336
													caa Gln		384
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													cca Pro		480
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			_			_	_		-		-		cag G1n		576
						_	_		-				tca Ser		624
					-	_		_	_				ata Ile	_	672
•						-			_			_	gaa Glu		720

			aac Asn								768
			tca Ser				_		_	-	816
			gaa Glu			-	-	-	_		864
			tat Tyr 295					_	_		912
		-	 gag G1u	 _	_			_	_	_	960
			gct Ala								1008
			tct Ser								1056
			tgt Cys					-			1104
			tat Tyr 375								1152
			tat Tyr								1200
			gaa Glu		-						1248

			caa G1n							_		•	1296
	-		att Ile				-	_					1344
			gaa Glu				_					 _	1392
-	-	_	ggt Gly 470	_	_			-	-		-	_	1440
			aat Asn	-	_				_			_	1488
			gat Asp	_		-	_	-					1536
			gag Glu										1584
			gac Asp										1632
			tat Tyr 550										1680
			agc Ser										1728
_		_	gaa Glu			-	_		-		-	-	1776

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1 Val Lys Glu Leu	Ala Ala Leu Lys 50	Ala Glu Leu 35 Tyr	Ala Leu 20 Leu Arg	5 Cys Thr Ser	Gln Tyr Ile Gly	Asn Ala Arg 55	Thr Asp 40 Ile	Pro 25 Asn Gly	10 Glu Ile Asn	Thr Leu Thr Leu	Phe Arg Ala 60	Leu Asn 45 Phe	Glu 30 Pro Ser	15 Ala Asn Thr	Ser Asp Arg Phe	
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Ser	Asn	He	Gln 180	His	Val	Leu	Val	Tyr 185	Glu	Asn	Pro	Ala	Leu 190	Gln	Glu
Lys	Ala	Leu 195	Ala	Cys	Ile	Pro	Va1 200	Gln	Glu	Leu	Lys	Arg 205		Ser	Gln
Glu	Lys 210	Leu	Ser	Arg	Ala	Arg 215	Lys	Leu	Asp	Lys	Gly 220	He	Asn ·	Пe	Ser
Asp 225	Glu	Asp	Phe	Leu	Leu 230	Leu	Glu	Leu	Leu	His 235	Trp	Phe	Lys		G1u 240
Phe	Phe	His	Trp	Val 245	Asn	Asn	Val	Leu	Cys 250	Ser	Lys	Cys	Gly		
Thr	Arg	Ser	Arg 260	Asp	Arg	Ser	Leu	Leu 265	Pro	Ser	Asp	Asp	G1u 270		Lys
Trp	Gly	A1a 275	Lys	Glu	Val	Glu	Asp 280	His	Tyr	Cys	Asp	Ala 285	Cys	Gln	Phe
Ser	Asn 290	Arg	Phe	Pro	Arg	Tyr 295	Asn	Asn	Pro	Glu	Lys 300	Leu	Leu	Glu	Thr
Arg 305	Cys	Gly	Arg	Cys	Gly 310	Glu	Trp	Ala	Asn	Cys 315	Phe	Thr	Leu	Cys	Cys 320
Arg	Ala	Vaì	Gly	Phe 325	Glu	Ala	Arg	Tyr	Val 330	Trp	Asp	Tyr	Thr	Asp 335	His
Val	Trp	Thr	G1u 340	Val	Tyr	Ser	Pro	Ser 345	Gln	Gln	Arg	Trp	Leu 350	His	Cys
Asp	Ala	Cys 355	Glu	Asp	Val	Cys	Asp 360	Lys	Pro	Leu	Leu	Tyr 365	Glu	Ile	Gly
Trp	Gly 370	Lys	Lys	Leu	Ser	Tyr 375	Val	He	Ala	Phe	Ser 380	Lys	Asp	Glu	Val
Va1 385	Asp	Val	Thr	Trp	Arg 390	Tyr	Ser	Cys	Lys	His 395	Glu	Glu	Val	He	Ala 400
Arg	Arg	Thr	Lys	Va1 405	Lys	Glu	Ala	Leu	Leu 410	Arg	Asp	Thr	Ile	Asn 415	Gly
Leu	Asn	Lys	G1n 420	Arg	Gln	Leu	Phe	Leu 425	Ser	Glu	Asn	Arg	Arg 430	Lys	Glu
Leu	Leu	G1n 435	Arg	Пe	Ile	Val	G1u 440	Leu	Val	Glu	Phe	11e 445	Ser	Pro	Lys
Thr	Pro 450	Lys	Pro	Gly	Glu	Leu 455	Gly	Gly	Arg	He	Ser 460	Gly	Ser	Val	Ala
Trp 465	Arg	Val	Ala	Arg	Gly 470	Glu	Met	Gly	Leu	G1n 475	Arg	Lys	Glu	Thr	Leu 480
Phe	He	Pro	Cys	G1u 485	Asn	Glu	Lys	He	Ser 490	Lys	Gln	Leu	Ḥis	Leu 495	Cys
Tyr	Asn	He	Va1 500	Lys	Asp	Arg	Tyr	Va1 505	Arg	Val	Ser	Asn	Asn 510	Asn	Gln

Thr	Ile	Ser 515	Gly	Trp	Glu	Asn	G1y 520	Val	Trp	Lys	Met	G1u 525	Ser	He	Phe	
Arg	Lys 530	Val	Glu	Thr	Asp	Trp 535	His	Met	Val	Tyr	Leu 540	Ala	Arg	Lys	Glu	
G1y 545	Ser	Ser	Phe	Ala	Tyr 550	He	Ser	Trp	Lys	Phe 555	Glu	Cys	Gly	Ser	Va1 560	
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	Thr		580					585					590			
	Leu	595					600					605				
	Thr 610					615					620	_	,	•	•	
625	Ala	·			630					635				Asp	His 640	
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Met	Ser			Trp					Leu		_	_	_	Asp	-	
1				5					10					15		
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Sei	Glu	Ser	20	ASII	пр	ыу	cys	25	ыу	ASII	He	um	30	Leu	ASP	
acc	cct	gga	gca	tct	tgt	999	att	gga	aga	cgt	cac	ggc	ctg	aac	tac	144
Thr	Pro	G1 <i>y</i> 35	Ala	Ser	Cys	Gly	Ile 40	Gly	Arg	Arg	His	Gly 45	Leu	Asn	Tyr	
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Cys	Gly 50	Val	Arg	Ala	Ser	Glu 55	Arg	Leu	Ala	Glu	Ile 60	Asp	Met	Pro	Tyr	

ctg Leu												-		_	240
gat Asp															288
aaa Lys		_	-		_		-			_	•	-	_	•	336
ggc Gly			-						-			_	•		384
aca Thr 130							-			-		_			432
cca Pro					-	-		_	-				-	_	480
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161

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Cys Gly Val Arg Ala Ser Glu Arg Leu Ala Glu Ile Asp Met Pro Tyr
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Leu Leu Lys Tyr Gln Pro Met Met Gln Thr Ile Gly Gln Lys Tyr Cys
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Asp Lys Ile Leu Val Asn Met Gly Asp Arg Thr Ser Met Val Gln Asp
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Pro Gly Ser Gln Ala Pro Thr Ser Trp Ile Ser Glu Ser Gln Val Ser
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                                                125
Gln Thr Thr Glu Val Leu Thr Thr Arg Ile Lys Glu Ile Gln Arg Arg
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Phe Pro Thr Trp Thr Pro Asp Gln Tyr Leu Arg Gly Gly Leu Cys Ala
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				999 Gly	_	_		-	_	-			144
_	_	-	-	gaa G1u 55	 			_	-				192
				gcc Ala									240
				aag Lys							_	-	288
				gag Glu									.336
				ggc Gly									384
				tca Ser 135	_		_		-	_	_	-	432
				agt Ser									480
				tcc Ser		-					-	_	528
				ctc Leu									576

ccg Pro											624
ccc Pro 210											672
gac Asp								_	 _	 _	720
ggt Gly											768
tat Tyr							Glu				816
ctg Leu											864
ctc Leu 290											912
tgg Trp				-	tga *						933
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Val	Gly	A1 a 35	Leu	Pro	Arg	Gly	Pro 40	Arg	Gln	Asn	Ser	Arg 45	Leu	Gly	Leu
Pro	Leu 50	Leu	Leu	Met	Pro	Glu 55	Glu	Ala	Arg	Leu	Leu 60	Ala	Glu	He	Gly
A1a 65	Val	Thr	Leu	Val	Ser 70	Ala	Pro	Arg	Pro	Asp 75	Ser	Arg	His	His	Ser 80
Leu	Ala	Leu	Thr	Ser 85	Phe	Lys	Arg	Xaa	G1n 90	Glu	Glu	Ser	Phe	G1n 95	Glu
G1n	Ser	Ala	Leu 100	Ala	Ala	Glu	Ala	Arg 105	Glu	Thr	Arg	Arg	Gln 110	Glu	Leu
Leu	Glu	Lys 115	He	Thr	Glu	Gly	G1n 120	Ala	Ala	Lys	Lys	G1n 125	Lys	Leu	Glu
	130					135		Gln			140				
145					150			Gly		155					160
Glu	Ala	Gly	Pro	Ser 165	Ser	Ser	Gln	Ala	Gly 170	Pro	Ser	Asn	Gly	Va1 175	Ala
Pro	Leu	Pro	Arg 180	Ser	Ala	Leu	Leu	Val 185	Gln	Leu	Ala	Thr	Ala 190	Arg	Pro
		195					200	Asp	·			205		·	•
	210				_	215		His			220	•			-
225					230			Phe		235					240
Gly	Gly	Asp	Phe	Leu 245		Tyr	Pro	Gly	-			-	Phe	His 255	
His	Tyr	Пe	A1a 260	Gln	Cys	Trp	Ala	Pro 265	Glu	Asp	Thr	He	Pro 270	Leu	Gln
Asp	Leu	Va1 275	Ala	Ala	Gly	Arg	Leu 280	Gly	Thr	Ser	Val	Arg 285	Lys	Thr	Leu
Leu	Leu 290	Cys	Ser	Pro	Gln	Pro 295	Asp	Gly	Lys	Val	Va1 300	Tyr	Thr	Ser	Leu
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			tca Ser								4	80
			gag Glu								5	28
			ctc Leu 180						 _		5	76
			ttc Phe								6	24
			ctc Leu								6	72
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Thr	Arg	Lys 35	Asn	Ser	Pro	Leu	His 40	Tyr	Tyr	Gln	Arg	Leu 45	Glu	Пе	Val
Glu	A1a 50	Ala	Пе	Arg	Thr	Leu 55	Phe	Ser	Val	Thr	Gly 60	Ile	Leu	Ala	Glu
Gln 65	Phe	Val	Pro	Asp	G1y 70	Pro	His	Leu	His	Leu 75		His	Glu	Asn	His 80
Trp	He	Lys	Leu	Met 85	Asn	Trp	Gln	His	Ser 90	Thr	Met	Tyr	Leu	Phe 95	Phe
Ala	Val	Ser	Gly 100	He	Val	Asp	Met	Leu 105	Thr	Tyr	Leu	Val	Ser 110	His	Val
Pro	Leu	Gly 115	Val	Asp	Arg	Leu	Val 120	Met	Ala	Val	Ala	Va1 125	Phe	Met	Glu
Gly	Phe 130	Leu	Phe	Tyr	Tyr	His 135	Val	His	Asn	Arg	Pro 140	Pro	Leu	Asp	Gln
His 145	He	His	Ser	Leu	Leu 150	Leu	Tyr	Ala	Leu	Phe 155	Gly	Gly	Cys	Val	Ser 160
Пe	Ser	Leu	Glu	Val 165	He	Phe	Arg	Asp	His 170	IJе	Val	Leu	Glu	Leu 175	Phe
Arg	Thr	Ser	Leu 180	He	He	Leu	Gln	Gly 185	Thr	Trp	Phe	Trp	Gln 190	He	Gly
Phe	Val	Leu 195	Phe	Pro	Pro	Phe	Gly 200	Thr	Pro	Glu	Trp	Asp 205	Gln	Lys	Asp
Asp	Ala 210	Asn	Leu	Met	Phe	Ile 215	Thr	Met	Cys	Phe	Cys 220	Trp	His	Tyr	Leu
A1a 225	Ala	Leu	Ser	He	Val 230	Ala	Val	Asn	Tyr	Ser 235	Leu	Val	Tyr	Cys	Leu 240
Leu	Thr	Arg	Met	Lys 245	Arg	His	Gly	Arg	G1y 250	Glu	He	Пe	Gly	11e 255	Gln
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					tgg Trp							288
					aca Thr							336
					cag G1n							384
					cct Pro 135							432
			_		atg Met	 				-		480
					agt Ser							528

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atg acc gag gag ccg gag ctg agc ccc gcc tac ctg atc agc gag gcc Met Thr Glu Glu Pro Glu Leu Ser Pro Ala Tyr Leu Ile Ser Glu Ala 35 40 45	144
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						ggg Gly					-	_		_	-	. 144
						tac Tyr 55										192
						atg Met										240
						ctg Leu										288
						aag Lys										336
						gtg Val										384
						aag Lys 135										432
ctg Leu 145	tgt Cys	gtt Val	acc Thr	aat Asn	gct Ala 150	atg Met	cga Arg	gaa Glu	gac Asp	ctg Leu 155	gcg Ala	gat Asp	aac Asn	tgg Trp	cac His 160	480
						tac Tyr										528
						cac His										576

		180			185				190			
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										acg Thr		672
										aca Thr		720
						-	_	_		gaa Glu 255		768
										ata Ile		816
										cag Gln	-	864
										gag Glu		912
										cac His		960
										ttc Phe 335		1008
	Leu									gag Glu		1056
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	210					215					220					
Leu	Arg	Glu	Arg	Pro	Ala	Leu	Leu	Val	Ser	Ser	Thr	Ser	Trp	Thr	Glu	
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Leu	Thr	Leu		Gly	His	Asn	Leu		Ser	Leu	Val	Cys		He	Thr	
0.3		0.3	260				_	265	_	_			270			
ыу	Lys	61y 275	Pro	Leu	Arg	Glu	1yr 280	lyr	Ser	Arg	Leu	1 le 285	His	GIn	Lys	
His	Phe 290	Gln	His	He	Gln	Va1 295	Cys	Thr	Pro	Trp	Leu 300	Glu	Ala	Glu	Asp	
Tyr	Pro	Leu	Leu	Leu	Gly	Ser	Ala	Asp	Leu	Gly	Val	Cys	Leu	His	Thr	
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Ser	Ser	Ser	Gly	Leu 325	Asp	Leu	Pro	Met	Lys 330	Val	Val	Asp	Met	Phe 335	Gly	
Cys	Cys	Leu	Pro	Val	Cys	Ala	Val	Asn	Phe	Lys	Cys	Leu	His		Leu	
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Val	Lys	His 355	Glu	Glu	Asn	Gly	Leu 360	Val	Phe	Glu	Asp	Ser 365	Glu	Glu	Leu	
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			gct Ala	-					_		2	1 32
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			tta Leu								5	528
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			gaa Glu								ϵ	524

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Cys	Phe	Pro 35	Gly	Leu	Gly	Val	Ser 40	Arg	His	Arg	Gln	G1n 45	Gln	His	His
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		Leu		85					90					95	
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		Leu 115					120					125			
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		Pro		165					170					175	
		Val	180					185					190	•	
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					gtc Val 70											240	
					aat Asn											288	
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atg	aaa	ctt	cat	cat	ggt	gag	aac	cgt	ctg	aag	aaa	ctc	atg	tgt	tgt	384	

Met	Lys	Leu 115	His	His	Gly	Glu	Asn 120	Arg	Leu	Lys	Lys	Leu 125	Met	Cys	Cys	
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	ttc Phe															624
	cnt Xaa 210															672
tta Leu 225	ctt Leu	gat Asp	gtt Val	cat His	gga Gly 230	gag G1u	gaa G1u	att Ile	gag G1u	ggc Gly 235	agg Arg	cta Leu	caa G1n	gaa Glu	999 Gly 240	720
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	ccc Pro			Lys												816
	tcc Ser															864
ctc	cac	ctt	cat	cag	aat	ggc	gtg	gaa	atg	ctc	atg	gaa	aat	gaa	gga	912

Leu His Leu His Gln Asn Gly Val Glu Met Leu Met Glu Asn Glu Gly 290 295 300	
ccc cag tca gga acc aac aag cca agg gaa acc tgc cag ggc cct gag Pro Gln Ser Gly Thr Asn Lys Pro Arg Glu Thr Cys Gln Gly Pro Glu 305 310 315 320	960
tgt cct ggc ctc cac acg ttt ctc ttg tgg tcc cat tca ggc ttt aac Cys Pro Gly Leu His Thr Phe Leu Leu Trp Ser His Ser Gly Phe Asn 325 330 335	1008
tgc ctg ctt tgt gca gag atg ctg gga cgg aaa gag gac ctc ctc cac Cys Leu Leu Cys Ala Glu Met Leu Gly Arg Lys Glu Asp Leu Leu His 340 345 350	1056
cac tgg aag cac cag cat aac tgt gag gac cct tcc aaa ctg tgg gct His Trp Lys His Gln His Asn Cys Glu Asp Pro Ser Lys Leu Trp Ala 355 360 365	1104
att tta aat acg gtc tcc aac cag gga gtg atc gaa ctt tcc agt gaa Ile Leu Asn Thr Val Ser Asn Gln Gly Val Ile Glu Leu Ser Ser Glu 370 375 380	1152
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			180		Leu			185					190		
		195			Gln		200					205			
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305					Asn 310					315					320
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183

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		-	ggg Gly		_	_		-			_		528
		-	att Ile	-			_			_			576
			ttt Phe										624
			att Ile		-	-	-			-			672
	 _		ctc Leu 230	_		_	-	-	-	-		_	720
			cgt Arg										768
			tca Ser										816
			ttt Phe										864

			-		cac His				_					_	•	912
				_	gaa Glu 310		_				_					960
		_			tgt Cys	_		_				_	-		_	1008
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		-		-	cct Pro		-		_		-		_			1104
	_			_	agt Ser		-	_			_	-	-			1152
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				-	tta Leu			_		-						1248
					gġa Gly											1296
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	_				aag Lys				_	_		-	-			1392

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														aaa Lys		1680
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His	Gln	Trp 195	Phe	Tyr	Phe	Glu	Val 200	Ser	Gly	Met	Arg	Pro 205		Val	Ala
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cgt	ссс	cct	cga	tġt	tcc	cac	tgc	agt	gtc	tqt	gac	aac	tgt	gta	gaq		384

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											gca Ala					576
											acg Thr					624
											cag G1n 220					672
											tgc Cys					720
											tat Tyr					768
						-		-			ttc Phe		_		•	816
											gat Asp					864
gga	gag	ctg	agg	aga	aca	aag	tct	aag	gga	agc	ctg	gag	ata	aca	gag	912

Gly	G1u 290	Leu	Arg	Arg	Thr	Lys 295	Ser	Lys	Gly	Ser	Leu 300	Glu	Пe	Thr	Glu	
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														aat Asn 335		1008
														atg Met		1056
														atg Met		1104
														gag G1u		1152
														gag Glu		1200
														agt Ser 415		1248
														aag Lys		1296
ncc Xaa	cag G1n	ggc G1y 435	aca Thr	ggc Gly	ttt Phe	gag G1u	ctg Leu 440	ggc Gly	cag Gln	ttg Leu	caa G1n	tcc Ser 445	att Ile	cgt Arg	tca Ser	1344
														aca Thr		1392
aat	gga	agc	cta	tct	tat	gac	agc	ttg	ctc	aca	cct	tca	gac	agc	cct	1440

Asn Gly Ser Leu Ser Tyr Asp Ser Leu Leu Thr Pro Ser Asp Ser Pro 465 470 475 gat ttt gag tca gtg cag gca ggg ctg agc cag acc cac ctt tag 1485 Asp Phe Glu Ser Val Gln Ala Gly Leu Ser Gln Thr His Leu * 485 <210> 134 <211> 494 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(494) <223> Xaa = Any Amino Acid <400> 134 Met Pro Ala Glu Ser Gly Lys Arg Phe Lys Pro Ser Lys Tyr Val Pro 10 Val Ser Ala Ala Ala Ile Phe Leu Val Gly Ala Thr Thr Leu Phe Phe Ala Phe Thr Cys Pro Gly Leu Ser Leu Tyr Val Ser Pro Ala Val Pro 40 Ile Tyr Asn Ala Ile Met Phe Leu Phe Val Leu Ala Asn Phe Ser Met Ala Thr Phe Met Asp Pro Gly Ile Phe Pro Arg Ala Glu Glu Asp Glu 70 75 Asp Lys Glu Asp Asp Phe Arg Ala Pro Leu Tyr Lys Thr Val Glu Ile Lys Gly Ile Gln Val Arg Met Lys Trp Cys Ala Thr Cys Arg Phe Tyr 100 105 Arg Pro Pro Arg Cys Ser His Cys Ser Val Cys Asp Asn Cys Val Glu 120 Glu Phe Asp His His Cys Pro Trp Val Asn Asn Cys Ile Gly Arg Arg 135 Asn Tyr Arg Tyr Phe Phe Leu Phe Leu Leu Ser Leu Thr Ala His Ile 150 155 160 Met Gly Val Phe Gly Phe Gly Leu Leu Tyr Val Leu Tyr His Ile Glu 165 170 Glu Leu Ser Gly Val Arg Thr Ala Val Thr Met Ala Val Met Cys Val 180 185 Ala Gly Leu Phe Phe Ile Pro Val Ala Gly Leu Thr Gly Phe His Val

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225					230					235					240
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Lys	Lys	Glu	Lys 260	Thr	Пe	Val	He	Arg 265	Pro	Pro	Phe	Leu	Arg 270	Pro	Glu
Val	Ser	Asp 275	Gly	Gln	He	Thr	Val 280	Lys	He	Met	Asp	Asn 285	Gly	Пe	Gln
Gly	G1u 290	Leu	Arg	Arg	Thr	Lys 295	Ser	Lys	Gly	Ser	Leu 300	Glu	He	Thr	Glu
Ser	Gln	Ser	Ala	Asp	Ala	Glu	Pro	Pro	Pro	Pro	Pro	Lys	Pro	Asp	Leu
305					310					315					320
				325					330				Thr	335	
Asp	Ser	Ser	Leu 340	Leu	Ala	Lys	Asp	Ser 345	Pro	Pro	Thr	Pro	Thr 350	Met	Tyr
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His	Ser 370	Ser	Ser	Ala	Lys	Leu 375	Ser	Arg	Gly	Asp	Ser 380	Leu	Lys	Glu	Pro
Thr 385	Ser	He	Ala	Glu	Ser 390	Ser	Arg	His	Pro	Ser 395	Tyr	Arg	Ser	Glu	Pro 400
Ser	Leu	Glu	Pro	G1u 405	Ser	Phe	Arg	Ser	Pro 410	Thr	Phe	Gly	Lys	Ser 415	Phe
His	Phe	Asp	Pro 420	Leu	Ser	Ser	Gly	Ser 425	Arg	Ser	Ser	Ser	Leu 430	Lys	Ser
Xaa	Gln	Gly 435	Thr	Gly	Phe	Glu	Leu 440	Glý	Gln	Leu	Gln	Ser 445	He	Arg	Ser
Glu	Gly 450	Thr	Thr	Ser	Thr	Ser 455	Tyr	Lys	Ser	Leu	A1a 460	Asn	Gln	Thr	Arg
Asn 465	Gly	Ser	Leu	Ser	Tyr 470	Asp	Ser	Leu	Leu	Thr 475	Pro	Ser	Asp	Ser	Pro 480
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<212> DNA

<213> Homo sapiens

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196

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26

Cys Val Gly Ser Gly Thr Glu Ala Tyr Val Leu Val Leu Asp Pro His

20

25

30

tac tgg ggc act cca aaa agc ccc agt gaa cta cag gct gct ggg tgg
Tyr Trp Gly Thr Pro Lys Ser Pro Ser Glu Leu Gln Ala Ala Gly Trp
35 40 45

gtg ggc tgg caa gag gtg agt gca gcc ttt gac ccc aac tcc ttc tac 192 Val Gly Trp Gln Glu Val Ser Ala Ala Phe Asp Pro Asn Ser Phe Tyr 50 55 60

aac ctg tgc ttg acc agc ctt agc tcc caa cag cag cag cgc acc ttg
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gac tga 246 Asp *

<210> 136

<211> 81

<212> PRT

<213> Homo sapiens

<400> 136

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35 40 45

Val Gly Trp Gln Glu Val Ser Ala Ala Phe Asp Pro Asn Ser Phe Tyr 50 55 60

Asn Leu Cys Leu Thr Ser Leu Ser Ser Gln Gln Gln Arg Thr Leu

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197

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	ttg Leu 130																432
	gag Glu																480
	atc Ile																528
	aga Arg															•	552
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Leu	Ala	Ala	G1n 20	Pro	Pro	Ala	Ala	Ser 25	Gln	Gly	Ala	Gln	Thr 30	Pro	Gly		
Glu	Lys	A1 a 35		Ala	Ala	Ala	Thr 40		Lys	Ala	Ala	Pro 45		Trp	Leu		
Lys	Arg 50		Leu	Val	Trp	Lys 55		Arg	Pro	Ala	Ser 60		Arg	Ala	Gln		
Pro 65	Gly	Leu	Val	Gln	G1u 70		Ala	Gln	Pro	G1n 75		Ser	Thr	Ser	Glu 80		
	Pro	Trp	Asn	Thr 85		Пе	Pro	Leu			Cys	Trp	Asp				
Phe	Leu	Thr	Asn 100		Thr	Phe	Leu		90 Va1	Leu	Leu	Trp		95 Va1	Leu		
Leu	Gly			Val	Glu	Leu		105 Phe	Gly	Leu	Ala	-	110 Phe	Val	Leu		
Ser	Leu 130	115 Phe	Tyr	Trp	Met	Tyr 135	120 Val	Gly	Thr	Arg	-	125 Pro	Glu	Glu	Lys		
Lys	Glu	Gly	Glu	Lys	Ser		Tyr	Ser	Val	Phe	140 Asn	Pro	Gly	Cys	Glu		

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												tca Ser			288
												agt Ser 110			336

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		_	cct Pro 135						_		432
			aac Asn								480
			gct Ala		_		-	-		•	528
			ctg Leu								576
			ccg Pro								624
			aga Arg 215								672
			ctg Leu								720
			aac Asn							cag G1n	768
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Glu	Lys 50	Tyr	Arg	Ser	He	Arg 55	Ile	Gly	Asn	Thr	Ala 60	Phe	Ser	Thr	Arg	
Leu 65	Leu	Pro	Val	Arg	G1y 70	Ala	Va1	Glu	Cys	Leu 75	Phe	Glu	Met	Gly	Phe 80	
Glu	Glu	Gly	Glu	Thr 85	His	Leu	Пe	Phe	Pro 90	Lys	Lys	Ala	Ser	Va1 95	Glu	
Gln	Leu	Gln	Lys 100	He	Arg	Asp	Leu	11e 105	Ala	Пe	Glu	Arg	Ser 110	Ser	Arg	
Leu	Asp	Gly 115	Ser	Asn	Lys	Ser	His 120	Lys	Val	Lys	Ser	Ser 125	Gln	Gln	Pro	
Ala	Ala 130	Ser	Thr	Gln	Leu	Pro 135	Thr	Thr	Pro	Ser	Ser 140	Asn	Pro	Ser	Gly	
Leu 145	Asn	Gln	His	Thr	Arg 150	Asn	Arg	Gln	Gly	Gln 155	Ser	Ser	Asp	Pro	Pro 160	
Ser	Ala	Ser	Thr	Val 165	Ala	Ala	Asp	Ser	Ala 170	He	Leu	Glu	Val	Leu 175	Gln	
Ser	Asn	Ile	Gln 180	His	Val	Leu	Val	Tyr 185	Glu	Asn	Pro	Ala	Leu 190	Gln	Glu	
Lys	Ala	Leu 195	Ala	Çys	He	Pro	Val 200	Gln	Glu	Leu	Lys	Arg 205	Lys	Ser	Gln	
Glu	Lys 210	Leu	Ser	Arg	Ala	Arg 215	Lys	Leu	Asp	Lys	Gly 220	He	Asn	He	Ser	
Asp 225	Glu	Asp	Phe	Leu	Leu 230	Leu	Glu	Leu	Leu	His 235	Trp	Phe	Lys	Glu	G1u 240	
Phe	Phe	His	Trp	Val	Asn	Asn	Val	Leu	Cys	Ser	Lys	Cys	Gly	Gly	Gln	

245

Thr Arg Ser Arg Asp Arg Ser Leu Leu Pro Ser Asp Asp Glu Leu Lys

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Trp	Gly	A1a 275	Lys	Glu	Val	Glu	Asp 280	His	Tyr	Cys	Asp	A1 a 285	Cys	Gln	Phe	
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							tca Ser									240
							aac Asn									288
							ggt Gly									336

									cta Leu		384
									caa G1n		432
									gaa Glu		480
				 _					gac Asp 175		528
							-		cag G1n		576
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									gac Asp		96
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									gag Glu		240
									gcc Ala 95		288
								-	gac Asp		336
									ggg Gly		384
									cgg Arg		432
									tgc Cys		480
									ctg Leu		528

				165					170					175		
											tcc Ser					576
											cgg Arg			_		624
					-	-		-			ctc Leu 220			_		672
											gag G1u					720
											ggc Gly					768
											gtg Val					816
-	gat Asp		-				_	_	tga *							846
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	Thr	35					40					45			
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65	Ala				70					75					80
	Phe			85					90					95	
	Arg		100					105					110		
	Asp	115					120					125			
	Pro 130					135					140				
145	Arg				150					155			,		160
	Thr			165					170					175	
	Gly		180					185					190		-
	Glu	195					200					205			
	Ser 210					215					220				
225	Thr				230					235					240
	Asp			245					250				•	255	
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					_	tct Ser		-						_		288
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					-	tgc Cys							-			384
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						tgg Trp										480
						atc Ile										528

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-		-			-			_	gcg Ala			 -	•		624
							_	_	gcc Ala		_				672
									agg Arg					_	720
_	_		-	-	_	_	_		ctg Leu 250	_					768
									ttt Phe	-					816
								_	ggc Gly				•		864
									ctg Leu						912
							-		ctg Leu	_		_			960
									act Thr 330						1008
									gcc Ala						1056

						ccc Pro							-	_		1104
		_			_	gct Ala 375		-						-		1152
						cta Leu				_			_	_	_	1200
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						gtg Val							-			1296
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	Gly	Leu	Glu 20	Leu	Ser	Arg	Cys	Arg 25		Lys	Pro	Pro	G1y 30		Ala	
Cys	Ser	Asn 35		Ser	Phe	Leu	Arg 40		Gln	Leu	Asp	Phe 45		Gln	Val	
Tyr	Phe 50		Ala	Leu	Ala	A1a 55	_	Trp	Leu	Gln	A1a 60		Tyr	Leu	Tyr	

Lys 65	Leu	Tyr	Gln	His	Tyr 70	Tyr	Phe	Leu	Glu	Gly 75	Gln	He	Ala	He	Leu 80
Tyr	Val	Cys	Gly	Leu 85	Ala	Ser	Thr	Val	Leu 90	Phe	Gly	Leu	Val	A1a 95	Ser
Ser	Leu	Val	Asp 100	Trp	Leu	Gly	Arg	Lys 105	Asn	Ser	Cys	Val	Leu 110	Phe	Ser
Leu	Thr	Tyr 115	Ser	Leu	Cys	Cys	Leu 120	Thr	Lys	Leu	Ser	Gln 125	Asp	Tyr	Phe
Val	Leu 130	Leu	Val	Gly	Arg	Ala 135	Leu	Gly	Gly	Leu	Ser 140	Thr	Ala	Leu	Leu
Phe	Ser	Ala	Phe	Glu	Ala	Trp	Tyr	He	His	Glu	His	Val	Glu	Arg	His
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				165	-				170					Ala 175	
Trp	Asn	His	Val 180	Leu	Ala	Val	Val	Ala 185	Gly	Val	Ala	Ala	G1u 190	Ala	Val
Ala	Ser	Trp 195	He	Gly	Leu	Gly	Pro 200	Val	Ala	Pro	Phe	Va1 205	Ala	Ala	He
Pro	Leu 210	Leu	Ala	Leu	Ala	Gly 215	Ala	Leu	Ala	Leu	Arg 220	Asn	Trp	Gly	Glu
Asn 225	Tyr	Asp	Arg	Gln	Arg 230	Ala	Phe	Ser	Arg	Thr 235	Cys	Ala	Gly	Gly	Leu 240
Arg	Cys	Leu	Leu	Ser 245	Asp	Arg	Arg	Val	Leu 250	Leu	Leu	Gly	Thr	Ile 255	Gln
Ala	Leu	Phe	Glu 260	Ser	Val	Ile	Phe	Ile 265	Phe	Val	Phe	Leu	Trp 270	Thr	Pro
Val	Leu	Asp 275	Pro	His	Gly	Ala	Pro 280	Leu	Gly	Ile	He	Phe 285	Ser	Ser	Phe
Met	Ala 290	Ala	Ser	Leu	Leu	Gly 295	Ser	Ser	Leu	Tyr	Arg 300	He	Ala	Thr	Ser
Lys 305	Arg	Tyr	His	Leu	Gln 310	Pro	Met	His	Leu	Leu 315	Ser	Leu	Ala	Val	Leu 320
Ile	Val	Val	Phe	Ser 325	Leu	Phe	Met	Leu	Thr 330	Phe	Ser	Thr	Ser	Pro 335	Gly
Gln	Glu	Ser	Pro 340	Val	Glu	Ser	Phe	11e 345		Phe	Leu	Leu	Ile 350	Glu	Leu
Ala	Cys	Gly 355	Leu	Tyr	Phe	Pro	Ser 360		Ser	Phe	Leu	Arg 365		Lys	Val
Пe	Pro 370	Glu	Thr	Glu	Gln	A1a 375		Val	Leu	Asn	Trp 380		Arg	Val	Pro
Leu 385		Ser	Leu	Ala	Cys 390		Gly	Leu	Leu	Val 395		His	Asp	Ser	Asp 400
	Lys	Thr	Gly	Thr 405		Asn	Met	Phe	Ser		Cys	Ser	Ala	Val 415	

Val	Met	Ala	Leu 420	Leu	Ala	Val	Val	Gly 425	Leu	Phe	Thr	Val	Va1 430	Arg	His	
Asp	Ala	G1u 435	Leu	Arg	Val	Pro	Ser 440		Thr	Glu	Glu	Pro 445		Ala	Pro	
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gcg	ctg	gcg	agg	ttt	tac	tgc	tac	act	gag	agg	acc	att	gcg	aag	ngg	144
			Arg													
		35					40					45				
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tac	tct	tcc	ctc	ctc	atc	cca	aac	ctc	acc	tac	acc	cad	cac	can	ana	240
			Leu													240
65	.	•••			70		u.,	LCU	••••	75	••••	4111	/ u g	u III	80	
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			gga													288
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1 Leu Ala Leu Cys 65 Arg Arg	Ala Tyr Leu Val 50 Ser Cys Ser Pro	Gly Gln Ala 35 Leu Ser Arg Gln Glu 115	Arg Arg Leu Gly Arg 100 Ala	-5 Ala Phe Arg Leu Gln 85 Phe Gln	His Tyr Asp Val 70 Arg Leu Leu	Cys Cys Pro 55 Pro Trp Asn Gly	Val Tyr 40 Ser Gly Thr Asp Ser 120	Leu 25 Thr Val Leu Val Pro 105 Gln	10 Ala Glu Lys Thr Gln 90 Gly Ala	Gln Arg Arg Cys 75 Thr His	Asp Thr Thr 60 Thr Cys Leu Ser	Pro Ile 45 Leu Gln Leu Leu	Glu 30 Ala Cys Arg Thr Trp 110 Pro	15 Asn Lys Arg Gln Cys 95 Gly Leu	Gln Xaa Gly Arg 80 Gln Asp	

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	gct Ala 50										192
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Gln Ala Val Glu Arg His Val Leu Pro Ile Leu Trp His Phe Leu Asn 50 55 60

Thr Ala Thr Arg Asn Gly Thr Leu Pro Gly Pro Ser Gly Asn Ile Arg 65 70 75 80

Gly Val Val Cys Arg Leu Ser Arg Ser Leu Gln Glu His His Gly Leu 85 90 95

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48

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											cgg Arg					240
											agt Ser					288
											ggc Gly					336
											cgg Arg					384
											cag Gln 140					432
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Ala Thr Asp Pro Thr Ser Pro Gln Pro His Asn Trp Val Trp Leu Gly
Thr Asp Gln Glu Glu Leu Ser Arg Gln Leu Asp Arg Gln Ser Pro Gly
Pro Pro Lys Gly Glu Gly Ser Cys Pro Cys Glu Ser Gly Gly Gly
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Glu Ala Pro Thr Leu Ala Pro Gly Pro Pro Gly Gly Thr Thr Ser Ser
                                105
Ser Ser Thr Leu Ala Arg Lys Glu Ala Gly Gly Arg Arg Lys Arg Val
        115
                            120
Glu Phe Val Thr Phe Ala Pro Ala Pro Pro Ala Gln Ser Pro Glu Glu
                        135
                                            140
Pro Val Gly Ala Pro Ala Val Gln Ser Ile Leu Val Ala Gly Glu Glu
                    150
                                        155
Asp Ile Arg Trp Val Cys Glu Asp Met Gly Leu Lys Asp Pro Glu Glu
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Leu Arg Asn Tyr Met Glu Arg Ile Arg Gly Ser Ser
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				c tgt gat gt u Cys Asp Va O	
cag gaa gat Gln Glu Asp 65				c atc cgc cg r Ile Arg Ar	
ggc cgc ctg Gly Arg Leu		-			o Pro
Gln Arg Pro			Gly Phe Arg	c cag ctg ct g Gln Leu Le 110	, , ,
	-		-	c gcc ctc cc u Ala Leu Pr 125	
ctg cgg aag Leu Arg Lys 130				r Ser Leu Va	
gca atc ggc Ala Ile Gly 145					
gta aca gcc Val Thr Ala					^ Gly
gtc cga gtc Val Arg Val			Asn Ile Trp		

			gca Ala								-			_		624
			ccc Pro													672
			cag Gln										-		-	720
	aac Asn		tcg Ser	tga *												735
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Gly	Gly	Arg	G1y 20	He	Gly	Ala	Gly	11e 25	Val	Arg	Ala	Phe	Va1 30	Asn	Ser	
Gly	Ala	Arg 35	Val	Val	Ile	Cys	Asp	Lys	Asp	<u>۸٦</u>	C	Clv	01	۸na	Ala	
Leu	C1						40	-	πор	GIU	5er	-	ыу	Ary		
Gln		Gin	Glu	Leu	Pro		40 Ala				Leu	45	-	·	•	
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65 Gly Gln Leu	50 Glu Arg Arg Asn Arg	Asp Leu Pro Leu 115	Asp Asp Glu 100	Val Cys 85 Glu Gly	Lys 70 Val Thr	55 Thr Val Ser Tyr Asn	Ala Leu Asn Ala Thr 120	Val Val Asn Gln 105 Leu	Phe Ser Ala 90 Gly Thr	Ile Glu 75 Gly Phe Lys	Leu 60 Thr His Arg Leu Ser	45 Cys Ile His Gln Ala 125	Asp Arg Pro Leu 110 Leu	Val Arg Pro 95 Leu Pro	Thr Phe 80 Pro Glu Tyr	
65 Gly Gln Leu Leu	50 Glu Arg Arg Asn Arg 130	Asp Leu Pro Leu 115 Lys	Asp Asp Glu 100 Leu	Val Cys 85 Glu Gly Gln	Lys 70 Val Thr Thr	55 Thr Val Ser Tyr Asn 135	Ala Leu Asn Ala Thr 120 Val	Val Val Asn Gln 105 Leu Ile	Phe Ser Ala 90 Gly Thr Asn	Ile Glu 75 Gly Phe Lys Ile	Leu 60 Thr His Arg Leu Ser 140	45 Cys Ile His Gln Ala 125 Ser	Asp Arg Pro Leu 110 Leu Leu	Val Arg Pro 95 Leu Pro Val	Thr Phe 80 Pro Glu Tyr Gly	

Val	Thr A	A1a	Met	Thr 165	Lys	Ala	Leu	Ala	Leu 170	Asp	Glu	Ser	Pro	Tyr 175	Gly	
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Glu	Glu L	Leu 195	Ala	Ala	Leu	Met	Pro 200	Asp	Pro	Arg	Ala	Thr 205	Пe	Arg	Glu	
Gly	Met L 210	_eu	Pro	Ser	His	Trp 215	Ala	Ala	Trp	Ala	Ser 220	Pro	Leu	Arg	Ser	
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					gtg Val							-			-	336
					cgc Arg	_				_		_	-	_		384
					gtg Val											432
					gtg Val 150	-	-	-				_	_			480
					gtg Val											528
					ggc Gly											576
					caa Gln											624
					gtg Val						-			_		672
			-		tcg Ser 230		-	_	_	_		-	_	-		720
cca	agc	tgt	асс	gtg	ggc	ttc	tat	gct	gga	gac	agg	aag	gag	ttt	gag	768

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i le		Ser	Trp	Phe	Δla		His	Pro	Δra	Δla		Phe	GIV	Leu	Hic	

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Glu	Thr	Leu	Asn	Pro 165	Val	Tyr	Val	Pro	Cys 170	Val	Lys.	G1u	Leu	Leu 175	Arg
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225					Ser 230					235					240
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		tac Tyr							 -	336
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		gcg Ala								432
		acg Thr 150								480
		aag Lys	-	_	_					528

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Asn	Gln	Gln	Val	Leu 165	Lys	Glu	Ala	Ser	G1n 170	Met	Asn	Leu	Leu	Ala 175	Arg	
Val	Trp	Trp	Tyr 180	Arg	Pro	Phe	Gln	Tyr 185	Phe	Glu	Lys	Asn	Val 190	Gln	Gly	
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	gcc Ala			-			-		-	-			_		_	,	288
-	acc Thr													_		ļ	336

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	-				_								gga Gly		•	384
	_				-						_	_	agc Ser		-	432
_						_	_			_	-	-	gcc Ala	_	_	480
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										_		_	-	cct Pro		336
														aga Arg		384
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-		-		-	_		-	_	_	_	_			att Ile	~ ~	480
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_			-	-			-		-	-				gat Asp		624
			_		_				_	-	-			act Thr	_	672
														tgg Trp		720
												_		agg Arg 255		768

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					gct Ala											864
					act Thr											912
					cag Gln 310											960
					agt Ser											1008
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G1n 385	Glu	Thr	Val	Glu	Met 390	Asp	He	Arg	He	G1y 395	He	Val	Glu	His	Thr 400	
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Ala	Tyr	I1e 35	Arg	Arg	Cys	Ala	Cys 40		Ala	Ser	Ser	Asp 45		Ser	Pro		
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G1y 65		Ile	Lys	Tyr	Phe 70		Val	Asp	Phe	Tyr 75		Ala	Met	Asp	Asp 80		
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gag	ctc	g gg	gtc	ctt	ttc	ctc	cct	tca	gca	ttt	ggt	cta	gac	agt	ttc	864

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Asp	Leu	Ser	Glu	Thr 85	Asn	Val	Tyr	Leu	Ile 90	Gly	Ser	Thr	Pro	Gly 95	Arg	
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Glu	Ser	Lys	Thr	Pro 165	Gly	Lys	Ser	Ser	Val 170		Leu	Tyr	Leu	Ile 175		
Pro	Ser	Val	Glu 180	Asn	Val	Arg	Thr	Ser 185	Leu	G1u	Gly	Tyr	Pro 190		Gly	
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Phe Phe Thr Phe Cys Cys Gly Thr Cys Tyr His Arg Tyr Cys Cys Arg
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Phe Ser Pro Lys Thr Ile Ala Gly Ile Ala Ser Ala Val Ile Leu Phe
Val Ala Val Val Ala Thr Thr Ile Cys Cys Phe Leu Cys Ser Cys Cys
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Tyr Leu Tyr Arg Arg Arg Gln Gln Leu Gln Ser Pro Phe Glu Gly Gln
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Glu Ile Pro Met Thr Gly Ile Pro Val Gln Pro Val Tyr Pro Tyr Pro
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Gln Asp Pro Lys Ala Gly Pro Ala Pro Pro Gln Pro Gly Phe Met Tyr
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Pro Pro Ser Gly Pro Ala Pro Gln Tyr Pro Leu Tyr Pro Ala Gly Pro
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Ser Thr Thr Val Ser Arg Lys Ala Trp Gly Ala Glu Ala Val Gly Cys 50 55 60

Ser Ile Gln Leu Thr Thr Pro Val Asn Val Leu Val Ile His His Val 65 70 75 80

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Phe	G1y	Glu	Gly 100	Leu	Thr	Met	Lys	Lys 105	Gln	Ser	Gly	Met	His 110	Leu	Thr
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Trp	He		He	Ala	Ala	Thr		Val	Ser	He	He		Val	Phe	Asp	
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1 Cys Trp	Asp	Arg Ile 35	Thr 20 Ile	5 Val Ala	Val Ala	Asn Thr	Gly Val 40	Ile 25 Val	10 Ile Ser	Ala Ile	Thr Ile	Val Ile 45	Val 30 Val	15 Val Phe	Ser Asp	
1 Cys Trp Pro Leu 65	Asp Ile Leu 50 Asp	Arg Ile 35 Gly Ser	Thr 20 Ile Gly His	5 Val Ala Lys Asp	Val Ala Met Ser 70	Asn Thr Ala 55 Ser	Gly Val 40 Pro Gln	Ile 25 Val Tyr Leu	10 Ile Ser Ser Leu	Ala Ile Ser Asn 75	Thr Ile Ala 60 Gly	Val Ile 45 Gly Leu	Val 30 Val Pro Lys	15 Val Phe Ser Thr	Ser Asp His Ala 80	
1 Cys Trp Pro Leu 65	Asp Ile Leu 50	Arg Ile 35 Gly Ser	Thr 20 Ile Gly His	5 Val Ala Lys Asp	Val Ala Met Ser 70	Asn Thr Ala 55 Ser	Gly Val 40 Pro Gln	Ile 25 Val Tyr Leu	10 Ile Ser Ser Leu	Ala Ile Ser Asn 75	Thr Ile Ala 60 Gly	Val Ile 45 Gly Leu	Val 30 Val Pro Lys	15 Val Phe Ser Thr	Ser Asp His Ala 80	
1 Cys Trp Pro Leu 65 Ala	Asp Ile Leu 50 Asp	Arg Ile 35 Gly Ser Ser	Thr 20 Ile Gly His	5 Val Ala Lys Asp Trp 85	Val Ala Met Ser 70 Glu	Asn Thr Ala 55 Ser Thr	Gly Val 40 Pro Gln Arg	Ile 25 Val Tyr Leu Ile	10 Ile Ser Ser Leu Lys 90	Ala Ile Ser Asn 75 Leu	Thr Ile Ala 60 Gly Leu	Val Ile 45 Gly Leu Cys	Val 30 Val Pro Lys Cys	15 Val Phe Ser Thr Cys 95	Ser Asp His Ala 80 Ile	
1 Cys Trp Pro Leu 65 Ala Gly Phe	Asp Ile Leu 50 Asp Thr Lys Ser	Arg Ile 35 Gly Ser Ser Asp Thr 115	Thr 20 Ile Gly His Val Asp 100 Tyr	5 Val Ala Lys Asp Trp 85 His	Val Ala Met Ser 70 Glu Thr	Asn Thr Ala 55 Ser Thr Arg	Gly Val 40 Pro Gln Arg Val Thr 120	Ile 25 Val Tyr Leu Ile Ala 105 Asp	10 Ile Ser Ser Leu Lys 90 Phe Leu	Ala Ile Ser Asn 75 Leu Ser Val	Thr Ile Ala 60 Gly Leu Ser Pro	Val Ile 45 Gly Leu Cys Thr Ser 125	Val 30 Val Pro Lys Cys Ala 110 Asp	15 Val Phe Ser Thr Cys 95 Glu Ile	Ser Asp His Ala 80 Ile Leu Ala	
1 Cys Trp Pro Leu 65 Ala Gly Phe	Asp Ile Leu 50 Asp Thr	Arg Ile 35 Gly Ser Asp Thr 115 Leu	Thr 20 Ile Gly His Val Asp 100 Tyr	5 Val Ala Lys Asp Trp 85 His Phe	Val Ala Met Ser 70 Glu Thr Ser Leu	Asn Thr Ala 55 Ser Thr Arg Asp His 135	Gly Val 40 Pro Gln Arg Val Thr 120 Gln	Ile 25 Val Tyr Leu Ile Ala 105 Asp	10 Ile Ser Ser Leu Lys 90 Phe Leu Gln	Ala Ile Ser Asn 75 Leu Ser Val	Thr Ile Ala 60 Gly Leu Ser Pro Asn 140	Val Ile 45 Gly Leu Cys Thr Ser 125 Ile	Val 30 Val Pro Lys Cys Ala 110 Asp	15 Val Phe Ser Thr Cys 95 Glu Ile Asn	Ser Asp His Ala 80 Ile Leu Ala Asn	

Ala	Asp	Leu	Asp	Ala 165	Glu	Leu	Glu	Asn	Cys 170	His	His	Tyr	Met	G1n 175	Phe
Ala	Ala	Ala	Ala 180	Tyr	Gly	Trp	Pro	Leu 185	Tyr	Пe	Tyr	Arg	Asn 190	Pro	Leu
Thr	Gly	Leu 195	Cys	Arg	He	Gly	Gly 200	Asp	Cys	Cys	Arg	Ser 205	Arg	Thr	Thr
Asp	Tyr 210	Asp	Leu	Val	Gly	Gly 215	Asp	Gln	Leu	Asn	Cys 220	His	Phe	Gly ·	Ser
I1e 225	Leu	His	Thr	Thr	Gly 230	Leu	Gln	Tyr	Arg	Asp 235	Phe	He	His	Val	Ser 240
Phe	His	Asp	Lys	Va1 245	Tyr	Glu	Leu	Pro	Phe 250	Leu	Val	Ala	Leu	Asp 255	His
			Ser 260					265					270		
		275	Thr				280					285			
Cys	G1u 290	Val	Gln	Asp	Arg	Leu 295	Ala	His	Lys	Gly	Ile 300	Ser	Gln	Ala	Ala
305			Tyr		310				·	315					320
			Ala	325					330					335	
			A1 a 340					345					350		-
		355	Arg			•	360					365		•	
	370		Gln			375					380				
385			Val		390					395				•	400
			He	405					410					415	
Lys	Пe	Leu	Leu 420	His	Gly	Leu	Trp	Tyr 425	Glu	Leu	Phe	Gly	G1y 430	Asn	Pro
Asn	Asn	Leu 435	Pro	Ser	Thr	Arg	G1y 440	Leu	Gln	Cys	Gly	Arg 445	Gly	Leu	Thr
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Leu 465	Asn														

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<212> DNA

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254

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1			_	5	•		•	·	10		·	·		15		
ata	gtt	gtc	gtt	gga	gga	tgt	gag	cga	gtt	gga	gga	ttt	aat	ctt	cca	96
He	Val	Val	Val	Gly	Gly	Cys	Glu	Arg	Val	Gly	Gly	Phe	Asn	Leu	Pro	
			20					25					30			
														ttg		144
Tyr	Thr		Cys	Tyr	Asp	Pro		Thr	Gly	Glu	Trp	•	Ser	Leu	Ala	
		35					40					45				
חבב	ctt	CCS	022	+++	300	222	tca	asa	tat	ac a	atc	tat	act	cta	200	192
														Leu		192
	50		a i u	· iic	****	55	JCI	ara	1,51	Alu	60	Cys	ΛIu	LCu	Ai g	
											00					
aat	gac	att	ctt	gtt	tca	ggt	gga	aga	atc	aac	agc	cqt	gat	gtc	tqq	240
														Val		
65	•				70		_	Ū		75			•		80	
														ctc		288
Пe	Tyr	Asn	Ser	Gln	Leu	Asn	He	Trp	Xaa	Arg	Val:	Ala	Ser	Leu	Asn	
				85					90				•	95		
												-		gta		336
_ys	ыу	Arg	•	Arg	HIS	Lys	met		vai	Leu	Leu	ыу	•	Val	lyr	
			100					105					110			
nt t	atc	aat	ממר	tat	nat	ana	Caa	aac	ana	ctt	acic	age	ata	gaa	tat	384
					_				_		•	_	_	Glu	_	304
	• 4 1	115	uı	131	ΛSP	J13	120	A311	רי א	Leu	Jei	125	vai	uiu	U) S	
		110					170					160				
tat	gat	tcc	ttt	tca	aat	cga	tgg	act	gaa	gtt	gct	ССС	ctt	aag	gaa	432
	-					-			-	_	_			_	-	

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Tyr	Asp 130	Ser	Phe	Ser	Asn	Arg 135	Trp	Thr	Glu	Val	Ala 140	Pro	Leu	Lys	Glu	
gcc Ala 145	gtg Val	agt Ser	tct Ser	cct Pro	gca Ala 150	gtg Val	act Thr	agc Ser	tgt Cys	gta Val 155	ggc Gly	aaa Lys	ctg Leu	ttt Phe	gtg Val 160	480
att Ile	ggt Gly	gga Gly	gga Gly	cct Pro 165	gat Asp	gat Asp	aat Asn	act Thr	tgt Cys 170	tct Ser	gat Asp	aag Lys	gtt Val	caa Gln 175	tct Ser	528
					aat Asn											57 <i>6</i>
					aca Thr											624
gcc Ala	ggt Gly 210	gga Gly	ctg Leu	acc Thr	aag Lys	gca Ala 215	ata Ile	tac Tyr	tgt Cys	tac Tyr	gat Asp 220	cca Pro	gtt Val	gaa G1u	gat Asp	672
tac Tyr 225	tgg Trp	atg Met	cac His	gta Val	cag Gln 230	aat Asn	aca Thr	ttc Phe	agc Ser	cgt Arg 235	cag G1n	gaa G1u	aac Asn	tgt Cys	ggt Gly 240	720
atg Met	tct Ser	gtg Val	tgt Cys	aat Asn 245	ggt Gly	aaa Lys	ata Ile	tat Tyr	atc Ile 250	ctg Leu	ggc Gly	gga Gly	aga Arg	cgg Arg 255	gaa G1u	768
aat Asn	gga Gly	gaa Glu	gcc Ala 260	aca Thr	gac Asp	act Thr	att Ile	ctc Leu 265	tgt Cys	tat Tyr	gat Asp	cct Pro	gca Ala 270	aca Thr	agt Ser	816
atc Ile	atc Ile	aca Thr 275	ggg Gly	gta. Val	gct Ala	gca Ala	atg Met 280	ccc Pro	agg Arg	cca Pro	gtg Val	tcc Ser 285	tat Tyr	cat His	ggc Gly	864
tgt Cys	gtg Val 290	act Thr	att Ile	cat His	aga Arg	tac Tyr 295	aat Asn	gag Glu	aaa Lys	tgc Cys	ttt Phe 300	aaa Lys	ctc Leu	tga *		909

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			260					265					270			
Ile	Ile	Thr 275		Val	Ala	Ala	Met 280		Arg	Pro	Val	Ser 285	270 Tyr	His	Gly	
Cys	Va1 290	Thr	Ile	His	Arg	Tyr 295	Asn	Glu	Lys	Cys	Phe 300	Lys	Leu			
	<2 <2	210> 211> 212> 213>	405 Dna	o sap	oiens	5										
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	ccg		cta		gga Gly											48
				-	gct Ala	-	-		_	-			_	-		96
					cgg Arg											144
					gag Glu			-								192
					ggc Gly 70											240
					gga Gly											288

	atg Met															336
	ccg Pro				_		-		_		-		-		_	384
_	gta Val 130		-	_	-	tag *										405
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1 Pro	Leu	His	Thr 20	5 Glu	Ala	Val	Val	Leu 25	10 Leu	Val	Pro	Ser	Asp 30	15 Asp	Gly	
	Ala	35	•				40	Phe				45	Arg			
Pro	Pro 50	Pro	Leu	He	Glu	Glu 55	Pro	Ala	Phe	Asn	Va1 60	Ser	Tyr	Thr	Arg .	
G1n 65	Pro	Pro	Asn	Pro	G1y 70	Pro	Gly	Ala	Gln	G1n 75	Pro	Gly	Pro	Pro	Tyr 80	
Tyr	Thr	Asp	Pro	G1y 85	Gly	Pro	Gly	Met	Asn 90	Pro	Val	Gly	Asn	Ser 95		
Ala	Met	Ala	Phe 100	Gln	Val	Pro	Pro	Asn 105	Ser	Pro	Gln	Gly	Ser 110	Val	Ala	
Cys	Pro	Pro 115	Pro	Pro	Ala	Tyr	Cys 120	Asn	Thr	Pro	Pro	Pro 125		Tyr	Glu	
Gln	Val 130	Val	Lys	Ala	Lys											

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												Gln				
1				5					10					15		
gtc	ttc	atc	ctg	999	gat	atc	ttt	gat	gaa	999	aag	tgg	agc	acc	cct	96
Val	Phe	He	Leu	Gly	Asp	He	Phe	Asp	Glu	Gly	Lys	Trp	Ser	Thr	Pro	
			20					25				·	30			
nag	gcc	tgg	gcg	gat	gat	gtg.	gag	cgg	ttt	cag	aaa	atg	ttc	aga	cac	144
Xaa	Ala	Trp	Ala	Asp	Asp	Val	Glu	Arg	Phe	Gln	Lys	Met	Phe	Arg	His	
		35					40					45				
												cat				192
Pro	Ser	His	Val	Gln	Leu	Lys	Val	Val	Ala	Gly	Asn	His	Asp	He	Gly	
	50					55					60					
												ttt				240
Phe	His	Tyr	Glu	Met	Asn	Thr	Tyr	Lys	Val	Glu	Arg	Phe	Glu	Lys	Val	
65					70					75					80	
												aac				288
Phe	Ser	Ser	Glu	Arg	Leu	Phe	Ser	Trp	Lys	Gly	He	Asn	Phe	Val	Met	
				85					90					95		
												atc				336
Val	Asn	Ser		Ala	Leu	Asn	Gly		Gly	Cys _.	Gly	He	Cys	Ser	Glu	
			100					105					110			
							_			-	_	aac	_		_	384
Ihr	Glu		Glu	Leu	He	Glu		Ser	His	Arg	Leu	Asn	Cys	Ser	Arg	
		115					120					125				

			cgg Arg 135							432
			cag Gln							480
			gac Asp							528
			gac Asp							576
			ccg Pro							624
			cac His 215							672
			aac Asn							720
		-	tac Tyr			-	_		_	768
			atc Ile							816
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_	-		aag Lys 295	-	_	•	tga *			900

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				245					250					255		
Glu	Asp	Val	Va1 260		He	He	Tyr	Cys 265		Val	Val	Gly	Phe 270		Val	
		275					Gly 280				Ser	Pro 285	Phe	Leu	Ser	
Gly	Leu 290	Asn	Leu	Leu	Gly	Lys 295	Arg	Lys	Thr	Arg						
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	<	220> 221> 222>	CDS	(4	453)									,		
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							cgt Arg									96
							tgt Cys 40									144
tcc Ser	aaa Lys 50	tgt Cys	tct Ser	tct Ser	ttt Phe	ctg Leu 55	gat Asp	tat Tyr	gtc Val	aga Arg	cgg Arg 60	tct Ser	cta Leu	aag Lys	aag Lys	192
							c t g Leu									240
tac Tyr	gag G1u	aag Lys	tat Tyr	aag Lys 85	cct Pro	cga Arg	atg Met	aat Asn	gag G1u 90	ctg Leu	gaa Glu	gct Ala	ttt Phe	aat Asn 95	atg Met	288
							tgt Cys									336

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100 105 110 cga ctt tgt tac ctg aaa gag cag gaa gat att gca tgg tct gct ctt 384 Arg Leu Cys Tyr Leu Lys Glu Gln Glu Asp Ile Ala Trp Ser Ala Leu 115 120 125 gtg aag ttg ttt gat ccc gtg aaa tct ccc aga tgt tat gct gtt att 432 Val Lys Leu Phe Asp Pro Val Lys Ser Pro Arg Cys Tyr Ala Val Ile 130 135 gcc ctg aag aag cag cag tga 453 Ala Leu Lys Lys Gln Gln * 145 150 <210> 186 <211> 150 <212> PRT <213> Homo sapiens <400> 186 Met Ser Ala Cys Leu Ala Leu Glu Arg Val Ala Ala Gly Gln Gly Leu Pro Thr Glu Ser Leu Phe Tyr Arg Ala Val Leu Gln Asp Ile Ile Lys 25 30 Asp Cys Tyr Gly Ile Thr Lys Cys Asp Arg His Val Gly Lys Ile Tyr 40 Ser Lys Cys Ser Ser Phe Leu Asp Tyr Val Arg Arg Ser Leu Lys Lys 55 Leu Gly Leu Asp Glu Ser Lys Leu Pro Glu Lys Ile Ile Met Asn Tyr 70 75 Tyr Glu Lys Tyr Lys Pro Arg Met Asn Glu Leu Glu Ala Phe Asn Met 90 Leu Lys Val Val Leu Ala Pro Cys Ile Glu Thr Leu Ile Leu Leu Asp 105 Arg Leu Cys Tyr Leu Lys Glu Gln Glu Asp Ile Ala Trp Ser Ala Leu 120 125 Val Lys Leu Phe Asp Pro Val Lys Ser Pro Arg Cys Tyr Ala Val Ile 130 135 140 Ala Leu Lys Lys Gln Gln 145 150 <210> 187

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		100>														
						tcc										48
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1				5					10					15		
ata	aac	tac	atc	ttc	cta	cta	a 2 a	663	0.20	oto	000	990	toa	000	ota	00
						ctg Leu										96
vai	uly	cys	20	FIIC	Leu	Leu	aiu	25	uiu	Leu	FIU	ury	30	Ald	Leu	
			20					23					30			
cac	tct	ctc	t.aa	agc	t.ca	ctg	tat	cta	aga	ccc	aca	cct	aca	ccc	cca	144
						Leu										1.
,		35					40		_,,			45				
gga	ССС	gtc	tcc	ссс	gag	ggc	cgg	ttg	gcg	gca	gcc	tgg	gac	gcg	ctt	192
						Gly										
	50					55					60	·	·			
															aat,	240
	Val	Arg	Pro	Val	Arg	Arg	Trp	Arg	Arg	Val	Ala	Val	Gly	Val	Asn	
65					70					75					80	
							_									
						ctc										288
Ala	Cys	Val	Asp		Val	Leu	Ser	Gly		Lys	Leu	Leu	Gln		Leu	
				85					90					95		
200	a++	a a t	oot	~~~	22+	~~~		+				_4				200
						ggg										336
зіу	Leu	361	100	diy	H211	Gly	Ly5	105	піз	ser.	пе	Leu		zei.	arg	
			100					105					110			
aat	gat	cta	กลล	gaa	acc	ttc	att	cac	ttc	ato	aaa	aan	oo a	ac a	act	384
						Phe										504
٠	ПОР	115	4,4	a.u	,,,,		120	1113	THE	TICE	uly	125	uiy	AIG	AIG	
												123				
gct	gaq	cgc	ttc	ttc	aqt	gat	aaq	qaa	act	ttt	cac	gac	att	qcc	cao	432
						Asp										.52
	130	•				135	•				140					

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	cca aag cta Pro Lys Leu 185		_	-	576
Pro Pro Glu	tca ttg cag Ser Leu Gln 200				624
	ggg gag gag Gly Glu Glu 215		n Leu Lys		672
	ttc tct cac Phe Ser His				720
	gtg tct agc Val Ser Ser		u Phe Gln		768
	ttg cac atg Leu His Met 265				816
Lys Arg Leu	ttg gag gtt Leu Glu Val 280				864
	cac cta gag His Leu Glu 295		r Met Thr		912
	gtc cat cag Val His Gln				960

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-	_	-	-						_	aaa Lys	-				-	1104
	-	-	_	_	-					cat His			_	-	-	1152
			-	_			_			tgg Trp 395	_		_	_	•	1200
-		-	-		-	-		-		aca Thr	-	_	Cys	-		1248
_			-		-	_			_	agg Arg						1296
_				_		-				att Ile	-					1344
		-	-				-			ata Ile						1392
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tag 1491

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Asn Met Leu Glu Val Phe Val Ser Ser Leu Glu Glu Phe Gln Pro Asp

Leu Val Val Leu Ser Gly Leu His Met Met Glu Gly Gln Ser Lys Glu

235

250

230

			260					265					270			
Leu	Gln	Arg 275	Lys	Arg	Leu	Leu	G1u 280	Val	Val	Thr	Ser	I1e 285		Asp	Пe	
Pro	Thr 290	Gly	Ile	Pro	Val	His 295	Leu	Glu	Leu	Ala	Ser 300	Met	Thr	Asn	Arg	
G1u 305	Leu	Met	Ser	Ser	Ile 310	Val	His	Gln	Val	Phe 315	Pro	Ala	Val	Thr	Ser 320	
Leu	Gly	Leu	Asn	G1u 325	Gln	Ġlu	Leu	Leu	Phe 330	Leu	Thr	Gln	Ser	Ala 335		
Gly	Pro	His	Ser 340	Ser	Leu	Ser	Ser	Trp 345	Asn	Gly	Val	Pro	Asp 350	Val	Gly	
Met	Val	Ser 355	Asp	Ile	Leu	Phe	Trp 360	He	Leu	Lys	Glu	His 365	Gly	Arg	Ser	
Lys	Ser 370	Arg	Ala	Ser	Asp	Leu 375	Thr	Arg	He	His	Phe 380	His	Thr	Leu	Val	
Tyr 385	His	He	Leu	Ala	Thr 390	Val	Asp	Gly	His	Trp 395	Ala	Asn	Gln	Leu	Ala 400	
Ala	Val	Ala	Ala	G1y 405	Ala	Arg	Val	Ala	Gly 410	Thr	Gln	Ala	Cys	Ala 415	Thr	
Glu	Thr	He	Asp 420	Thr	Ser	Arg	Val	Ser 425	Leu	Ąrg	Ala	Pro	G1n 430	Glu	Phe	
Met	Thr	Ser 435	His	Ser	Glu	Ala	G1y 440	Ser	Arg	He	Val	Leu 445	Asn	Pro	Asn	
Lys	Pro 450	Val	Val	Glu	Trp	His 455	Arg	Glu	Gly	Пe	Ser 460	Phe	His	Phe	Thr	
Pro 465	Val	Leu	Val	Cys	Lys 470	Asp	Pro	Ile	Arg	Thr 475	Val	Gly	Leu	Gly	Asp 480	
Ala	He	Ser	Ala	G1u 485	Gly	Leu	Phe	Tyr	Ser 490	Glu	Val	His	Pro	His 495	Tyr	
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	gcg Ala										144
	tgt Cys 50										192
	tac Tyr			_	_	_	-		-	_	240
	tgg Trp										288
	atc Ile										336
tga *											339

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<213> Homo sapiens

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Gly	He	Val	Val 100	Met	Ala	Asp	Pro	Lys 105	Gly	Lys	Ala	Tyr	Arg 110	Val	Val	
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				tgc Cys												96
				tgg Trp				-					_	-		144
				gga Gly												192
				gtt Val												240
				aag Lys 85					-		_	_		_		288
				gcc Ala												336

	tct Ser		_				_		_			-	384
	gag Glu 130			-			_			-	-		432
	acg Thr			_			 _	Asp		-	-	-	480
	gcc Ala			-	_	-			_			_	528
	ttc Phe					-		-		-	_		576
	cag G1n					_			_	_	_	_	624
ttg Leu	tga *												630

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Thr	Ser	G1u 115	Asp	Leu	Ile	Leu	Ile 120	Gly	Asn	Glu	Leu	Asp 125	Leu	Ala	Cys	
Gly	Glu 130	Arg	He	Arg	Leu	Glu 135	Lys	Val	Leu	Leu	Val 140	Gly	Ala	Asp	Asn	
Phe 145	Thr	Leu	Leu	Gly	Lys 150	Pro	Leu	Leu	Gly	Lys 155	Asp	Leu	Val	Arg	Val 160	
Glu	Ala	Thr	Val	Ile 165	Glu	Lys	Thr	Glu	Ser 170	Trp	Pro	Arg	Пe	Ile 175	Met	
Arg	Phe	Arg	Lys 180	Arg	Lys	Asn	Phe	Lys 185	Lys	Lys	Arg	He	Val 190	Thr	Thr	
Pro	Gln	Thr 195	Val	Leu	Arg	Ile	Asn 200	Ser	He	Glu	He	A1a 205	Pro	Cys	Leu	
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1	413	501	Al 9	5			110		10	501	.,,	110	••••	15	110	
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Pro	Gly	Ihr	A1a 20	Ala	Ala	Pro	Ala	Lys 25	Pro	Ala	Pro	Pro	A1a 30	Thr	Pro	
	gcg					_	-		_	-	_	_		-		144
Gly	Ala	Pro 35	Thr	Ser	Pro	Ala	G1u 40	His	Arg	Leu	Leu	Lys 45	Thr	Cys	Trp	
	tgt									-						192
Ser	Cys	Arg	Val	Leu	Ser	Gly	Leu	Gly	Leu	Met	Gly	Ala	Gly	Gly	Tyr	

	50					55					60					
	tac Tyr			-		-				_				_	-	240
	tgg Trp											-				288
	gcc Ala					-	_	-	-	-				_	_	336
	cgc Arg	_	-	tga *												351
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Met 1	<2	213> 100>	Homo 194	•			Pro	Phe	Glu 10	Ser	Tyr	Ile	Thr		Pro	
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l Pro Gly	<2	213> 400> Ser Thr Pro 35	Homo 194 Arg Ala 20 Thr	Leu 5 Ala Ser	Ser Ala Pro	Gln Pro Ala	Ala Glu 40	Lys 25 His	10 Pro Arg	Ala Leu Met	Pro Leu	Pro Lys 45	Ala 30 Thr	15 Thr Cys	Pro Trp	
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gtc Val										96
gag G1u										144
gag Glu 50										192
gcc Ala										240
ctg Leu										288
agc Ser										336
gtc Val										384
gac Asp 130										432

gca Ala											480
aag Lys								-			528
ctg Leu						_	-		Leu		576
aac Asn				-	-			_		•	624
ttt Phe 210			-				•			-	672
cca Pro											720
tct Ser											768
gga Gly											816
aca Thr											864
aat Asn 290											912
ttg Leu											960

tta att agt ttt att atg tat gct acc att cga act gag agt att cgg 1008 Leu Ile Ser Phe Ile Met Tyr Ala Thr Ile Arg Thr Glu Ser Ile Arg 325 330 335 tgg cta att cca gga caa gag cag gaa cat gtg gag tag 1047 Trp Leu Ile Pro Gly Gln Glu Gln Glu His Val Glu * 340 345 <210> 196 <211> 348 <212> PRT <213> Homo sapiens <400> 196 Met Arg Leu Leu Gly Trp Trp Gln Val Leu Leu Trp Val Leu Gly Leu Pro Val Arg Gly Val Glu Val Ala Glu Glu Ser Gly Arg Leu Trp Ser 25 Glu Glu Gln Pro Ala His Pro Leu Gln Val Gly Ala Val Tyr Leu Gly Glu Glu Glu Leu Leu His Asp Pro Met Gly Gln Asp Arg Ala Ala Glu Glu Ala Asn Ala Val Leu Gly Leu Asp Thr Gln Gly Asp His Met Val 75 Met Leu Ser Val Ile Pro Gly Glu Ala Glu Asp Lys Val Ser Ser Glu Pro Ser Gly Val Thr Cys Gly Ala Gly Gly Ala Glu Asp Ser Arg Cys 105 Asn Val Arg Glu Ser Leu Phe Ser Leu Asp Gly Ala Gly Ala His Phe 120 Pro Asp Arg Glu Glu Glu Tyr Tyr Thr Glu Pro Glu Val Ala Glu Ser 135 140 Asp Ala Ala Pro Thr Glu Asp Ser Asn Asn Thr Glu Ser Leu Lys Ser 150 Pro Lys Val Asn Cys Glu Glu Arg Asn Ile Thr Gly Leu Glu Asn Phe 165 170 Thr Leu Lys Ile Leu Asn Met Ser Gln Asp Leu Met Asp Phe Leu Asn 185 Pro Asn Gly Ser Asp Cys Thr Leu Val Leu Phe Tyr Thr Pro Trp Cys 200 Arg Phe Ser Ala Ser Leu Ala Pro His Phe Asn Ser Leu Pro Arg Ala 215 220 Phe Pro Ala Leu His Phe Leu Ala Leu Asp Ala Ser Gln His Ser Ser

225					230					235					240	•
Leu	Ser	Thr	Arg	Phe 245	Gly	Thr	Val	Ala	Va1 250	Pro	Asn	Пe	Leu	Leu 255	Phe	
Gln	Gly	Ala	Lys 260	Pro	Met	Ala	Arg	Phe 265	Asn	His	Thr	Asp	Arg 270	Thr	Leu	
Glu	Thr	Leu 275	Lys	He	Phe	He	Phe 280	Asn	Gln	Thr	Gly	Ile 285	Glu	Ala	Lys	
	290					295					300		Leu			
305					310					315			Leu		320	
				325		-			330	·		Glu	Ser	11e 335	Arg	
Trp	Leu	He	Pro 340	Gly	Gln	Glu	Gln	G1u 345	His	Val	Glu					
		210> 211>	197 444													
			DNA													
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			TIONK	<i>ս</i> Տալ	JICH.	3									-	
		220>														
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acg	cca	atg	act	gag	aat	gga	gaa	atc	aac	ttt	tca	gta	att	ggt	cag	96
													He			
			20			-		25					30	J		
								-			_		att			144
Tyr	Val	Asp 35	Tyr	Leu	Val	Lys	Glu 40	Gln	Gly	Val	Lys	Asn 45	Ile	Phe	Val	
													gag			192
Asn	Gly 50	Thr	Thr	Gly	Glu	Gly 55	Leu	Ser	Leu	Ser	Va1 60	Ser	Glu	Arg	Arg	
													ctg			240
Gln	Val	Ala	Glu	Glu	Trp	Val	Thr	Lys	Gly	Lys	Asp	Lys	Leu	Asp	Gln	

65					70					75					80	
					gga Gly											288
					gaa Glu											336
					cca Pro											384
					gcg Ala		-		_							432
	ctg Leu		tga *													444
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Met 1	Ala	Phe	Pro	Lys 5	Lys	Lys	Leu	Gln	Gly 10	Leu	Val	Ala	Ala	Thr 15	He	
Thr	Pro	Met	Thr 20	Glu	Asn	Gly	Glu	11e 25	Asn	Phe	Ser	Val	Ile 30	Gly	Gln	
Tyr	Val	Asp 35		Leu	Val	Lys	Glu 40		Gly	Val	Lys	Asn 45		Phe	Val	
Asn	G1y 50		Thr	Gly	Glu	G1 <i>y</i> 55	-	Ser	Leu	Ser	Va1 60		Glu	Arg	Arg	
G1n 65		Ala	Glu	Glu	Trp 70		Thr	Lys	Gly	Lys 75		Lys	Leu	Asp	Gln 80	
	Пе	Пe	His	Va1 85	Gly	Ala	Leu	Ser	Leu 90		Glu	Ser	Gln	G1u 95		
Ala	Gln	His	Ala 100		Glu	Пе	Gly	Ala 105		Gly	Пе	Ala	Val 110		Ala	
Pro	Phe	Phe		Lvs	Pro	Trp	Thr		Asn.	Πe	Leu	He		Phe	Leu	

Glu 130 Leu		Ala	Ala	Ala	Pro 135	120 Leu	Pro	Cys	His	Phe 140	125 I le	Thr	Ile	Thr	
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					cat His										144
					att Ile 55								-		192
					gtc Val						_				240
					ttt Phe										288

		tat ggt tac Tyr Gly Tyr 105		- •	
		cct gga tac Pro Gly Tyr 120		•	•
	_	cct aac aca Pro Asn Thr 135			~ ~
		tgg ggt gtt Trp Gly Val	•	-	
	-	cgg cat tat Arg His Tyr	_		Ala
		ctg ctg gtc Leu Leu Val 185	•		
	_	gtt ccc cca Val Pro Pro 200		•	
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Met Met Ser Gln Gly Ser Gln Phe Leu Tyr Ser Thr Phe Gly Tyr Thr

Glu Glu Asn Glu Pro Val Ile Tyr Asn Arg Ala Arg Phe Tyr Val Tyr 55

Asn Lys Lys Lys Arg Leu Val Asn Thr Pro Tyr Val Asp Asn Ser Tyr

Lys Trp Ala Gly Gly Gly Phe Leu Ser Thr Val Gly Asp Leu Leu Lys 90

Phe Gly Asn Ala Met Leu Tyr Gly Tyr Gln Val Gly Leu Phe Lys Asn 105

Ser Asn Glu Asn Leu Leu Pro Gly Tyr Leu Lys Pro Glu Thr Met Val 120

Met Met Trp Thr Pro Val Pro Asn Thr Glu Met Ser Trp Asp Lys Glu 135

Gly Lys Tyr Ala Met Ala Trp Gly Val Val Glu Xaa Lys Gln Thr Tyr 150 155

Gly Ser Cys Arg Lys Gln Arg His Tyr Ala Ser His Thr Gly Gly Ala 170

Val Gly Ala Ser Ser Val Leu Leu Val Leu Pro Glu Glu Leu Asp Thr 180 185

Glu Thr Ile Asn Asn Lys Val Pro Pro Arg Gly Ile Ile Val Ser Ile 200

Ile Cys Asn Met Gln Ser Val Gly Leu Asn Ser Thr Ala Leu Lys Ile 215 220

Ala Leu Glu Phe Asp Lys Asp Arg Ser Asp 225 230

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gtg aaa gcc cgc Val Lys Ala Arg			ys Thr Pro Arg		528
tct cgt tcc cat Ser Arg Ser His 180	Ser Gly Met			•	576
gga aac cag act Gly Asn Gln Thr 195					624
tta gca ctt ttg Leu Ala Leu Leu 210		Asp Lys Se			672
tac atc cat gtg Tyr Ile His Val 225					720
gcc atc tta aaa Ala Ile Leu Lys			et Thr Thr Leu		768
gaa atc agt tac Glu Ile Ser Tyr 260	Thr Gly Ser		le Glu Gly Gly		816
agc atc aga atg Ser Ile Arg Met 275					864
gaa aag aca gga Glu Lys Thr Gly 290			·		885

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gtt Val											96
ctc Leu											144
tct Ser 50											192
gct Ala											240
ctg Leu		Pro		Gly	Val	Ser	Val	Cys			288
gac Asp											336
ccc Pro											384
cca Pro											432

130			135			140					
							gtg Val	_	_		480
							ttc Phe				528
							gaç Asp				576
-	_			 _			gct Ala 205			_	624
							cca Pro				672
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<211> 286

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<213> Homo sapiens

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<211> 561

<212> DNA

<213> Homo sapiens

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-	tct Ser				_	_				taa *						5	661
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Ser	Phe	Ser	Asp 20	Gln	Leu	Pro	Gly	Thr 25	Met	Ala	Thr	Leu	Ser 30	Leu	Val		
Asn	Glu	A1 a 35	Gln	Tyr	Leu	Leu	11e 40	Asn	Thr	Ser	Ser	11e 45	Leu	Glu	Leu		
	50					55	·				60			Leu			
65					70					75				Ile	80		
				85					90					I1e 95			
			100					105					110	Met			
		115				_	120					125		Gln			
	130					135	-				140		-	Leu			
145					150					155				Gly	160		
Gln	Val	Leu	Pro	Val 165	Leu	Lys	Glu	Asn	Val 170	Glu	Gly	His	Asp	Leu 175	Pro		
Ala	Ser	Glu	Lys 180	His	Gln	Asp	Val	Thr 185	Ser								
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	tca Ser				_				-	_			_	_	•	144
-	gaa Glu 50								-	-	_	-	-			192
	cag G1n										_		_			240
	agt Ser						_			_	_	_			-	288
	tac Tyr								-		-					336
	caa G1n															384
	cca Pro						-	-	-	_			-	-		432

130				135			140				
			cac His 150								480
	_		cat His		-	-	-			~	528
			atc Ile								576
			gct Ala								624
			gaa G1u								672
			caa Gln 230				_	_	-		720
			att Ile							-	768
			ttc Phe				_				816
			gta Val								864
			tta Leu								912
			cct Pro					-	-		960

305 310 315 320 aca tgg ata gta act caa gta gca ata agt tac aca gtt gtg cca ttt 1008 Thr Trp Ile Val Thr Gln Val Ala Ile Ser Tyr Thr Val Val Pro Phe 325 330 335 gtg ctt ctt tct ata aaa cca tca ctc acg ttt tac agc tcc tgg tat 1056 Val Leu Leu Ser Ile Lys Pro Ser Leu Thr Phe Tyr Ser Ser Trp Tyr 340 345 tat tgc ctg cac att ctt ggt atc tta gta tta ttg ttg ttg cca gtg 1104 Tyr Cys Leu His Ile Leu Gly Ile Leu Val Leu Leu Leu Pro Val 355 360 365 aaa aaa act caa aga aga aag aat aca cat gaa aac att cag ctc tca 1152 Lys Lys Thr Gln Arg Arg Lys Asn Thr His Glu Asn Ile Gln Leu Ser 370 375 380 caa tcc aaa aag ttt gat gaa gga gaa aat tct ttg gga cag aac agt 1200 Gln Ser Lys Lys Phe Asp Glu Gly Glu Asn Ser Leu Gly Gln Asn Ser 385 390 395 ttt tct aca aca aac aat gtt tgc aat cag aat caa gaa ata gcc tcg 1248 Phe Ser Thr Thr Asn Asn Val Cys Asn Gln Asn Gln Glu Ile Ala Ser 405 410 415 aga cat tca tca cta aag cag tga 1272. Arg His Ser Ser Leu Lys Gln * 420 . <210> 208 <211> 423 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(423) <223> Xaa = Any Amino Acid <400> 208 Met His Asn Tyr Cys Phe Val Phe Ala Leu Gly Tyr Leu Thr Val Cys 10 15

Gln	Val	Thr	Arg 20	Val	Tyr	He	Phe	Asp 25	Tyr	Gly	Gln	Tyr	Ser 30	Ala	Asp
Phe	Ser	G1y 35	Pro	Met	Met	Пе	11e 40	Thr	Gln	Lys	He	Thr 45	Ser	Leu	Ala
Cys	Glu 50	He	His	Asp	Gly	Met 55	Phe	Arg	Lys	Asp	Glu 60	Glu	Leu	Thr	Ser
Ser 65	Gln	Arg	Asp	Leu	A1a 70	Val	Arg	Arg	Met	Pro 75	Ser	Leu	Leu	Glu	Tyr 80
Leu	Ser	Tyr	Asn	Cys 85	Asn	Phe	Met	Gly	I le 90	Leu	Ala	Xaa	Pro	Xaa 95	Cys
Ser	Tyr	Lys	Asp 100	Tyr	He	Thr	Phe	Ile 105	Glu	Gly	Arg	Ser	Tyr 110	His	He
Thr	Gln	Ser 115	Gly	Glu	Asn	Gly	Lys 120	Glu	Glu	Thr	Gln	Tyr 125	Glu	Arg	Thr
	130					Ala 135					140				
145					150	Leu				155					160
Tyr	Asn	He	Asp	G1u 165	His	Phe	Gln	Ala	Thr 170	Ala	Ser	Trp	Pro	Thr 175	Lys
Пe	He	Tyr	Leu 180	Tyr	Пe	Ser	Leu	Leu 185	Ala	Ala	Arg	Pro	Lys 190	Tyr	Tyr
		195				Asp	200					205	•		
Phe	Arg 210	Gly	Tyr	Asp	Glu	Asn 215	Gly	Ala	Ala	Arg	Trp 220	Asp	Leu	He	Ser
225					230	He				235					240
Leu	Asp	Asn	Trp	Asn 245	He	Gln	Thr	Ala	Leu 250	Trp	Leu	Lys	Arg	Va1 255	Cys
Tyr	Glu	Arg	Thr 260	Ser	Phe	Ser	Pro	Thr 265	He	Gln	Thr	Phe	I1e 270	Leu	Ser
		275				Tyr	280					285			
Gly	Va1 290	Leu	Met	Thr	Leu	A1a 295	Ala	Arg	Ala	Met	Arg 300	Asn	Asn	Phe	Arg
His 305	Tyr	Phe	He	Glu	Pro 310	Ser	Gln	Leu	Lys	Leu 315	Phe	Tyr	Asp	Val	11e 320
Thr	Trp	He	Val	Thr 325	Gln	Val	Ala	He	Ser 330	Tyr	Thr	Val	Val	Pro 335	Phe
Val	Leu	Leu	Ser 340	He	Lys	Pro	Ser	Leu 345	Thr	Phe	Tyr	Ser	Ser 350	Trp	Tyr
Tyr	Cys	Leu 355	His	He	Leu	Gly	Ile 360	Leu	Val	Leu	Leu	Leu 365	Leu	Pro	Val

Lys	Lys 370	Thr	Gln	Arg	Arg	Lys 375	Asn	Thr	His	Glu	Asn 380	Ile	Gln	Leu	Ser	
G1n 385	Ser	Lys	Lys	Phe	Asp 390	Glu	Gly	Gļu	Asn	Ser 395	Leu	Gly	Gln	Asn	Ser 400	
Phe	Ser	Thr	Thr	Asn 405	Asn	Val	Cys	Asn	G1n 410	Asn	Gln	Glu	Пе	Ala 415		
Arg	His	Ser	Ser 420	Leu	Lys	Gln								.10		
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										Arg						
										ctg Leu						96
										cgc Arg						144
										ccc Pro						192
		_	-	-				-		gat Asp 75	-			_		240
										ctg Leu						288
gtg	ctg	acc	agc	ctt	gtg	gcg	ctg	cgg	cgg	gag	gtg	gag	gag	ctg	aga	336

Val	Leu	Thr	Ser 100	Leu	Val	Ala	Leu	Arg 105	Arg	Glu	Val	Glu	Glu 110	Leu	Arg	
	agc Ser															384
	atg Met 130															432
	cgg Arg									-		-			~	480
	tcc Ser															528
	aca Thr															576
	gag Glu															624
	aag Lys 210															672
	gcc Ala															720
ctc Leu	ctg Leu	cag G1n	cag G1n	gcc Ala 245	gac Asp	gag G1u	ctg Leu	cac His	agg Arg 250	ggt Gly	gat Asp	gag Glu	caa G1n	ggc Gly 255	aag Lys	768
	gag Głu															816
cgg	cag	gac	ttt	ctc	tgg	cgc	ctg	gcc	cga	gcc	tac	agt	gac	atg	tgt	864

Arg	Gln	Asp 275	Phe	Leu	Trp	Arg	Leu 280	Ala	Arg	Ala	Tyr	Ser 285	Asp	Met	Cys	
						-		-	_			_		gat Asp		912
														gct Ala	gac Asp 320	960
		-								_	_	_		cat His 335		1008
						_						_		cat His		1056
-		-		-		_		-			_	-		ttt Phe		1104
						-	-			_	-			gaa Glu		1152
		-		-	_		_	-			_	•		gtg Val	•	1200
												-		gga Gly 415		1248
														cta Leu		1296
								_	-	-	_	-		ctg Leu		1344
gat	gtc	acg	aag	gag	gat	ttg	gct	atc	cag	aag	gac	ctg	gaa	gaa	ctg	1392

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Leu	Leu	GIn	GIn	A1a 245	Asp	Glu	Leu	His	Arg 250	Gly	Asp	Glu	Gln	G1 <i>y</i> 255	Lys	
Arg	Glu	Gly	Phe 260	Gln	Leu	Leu	Leu	Asn 265	Asn	Lys	Leu	Val	Tyr 270		Ser	
Arg	Gln	Asp 275	Phe	Leu	Trp	Arg	Leu 280	Ala	Arg	Ala	Tyr	Ser 285		Met	Cys	
Glu	Leu 290	Thr	Glu	Glu	Val	Ser 295	Glu	Lys	Lys	Ser	Tyr 300		Leu	Asp	Gly	
Lys 305	Glu	Glu	Ala	Glu	Ala 310	Ala	Leu	Glu	Lys	Gly 315	Asp	Glu	Ser	Ala	Asp 320	
	His	Leu	Trp	Tyr 325		Val	Leu	Cys	Gly 330		Leu	Ala	Glu	His 335		
Ser	Ile	Gln	Arg 340		Пe	Gln	Ser	Gly 345		Ser	Phe	Lys	G1u 350		Val	
Asp	Lys	A1 a 355		Ala	Leu	Gln	Pro 360		Asn	Pro	Met	A1a 365		Phe	Leu	
Leu	Gly 370		Trp	Cys	Tyr	G1n 375		Ser	His	Leu	Ser 380		Leu	Glu	Lys	
Lys 385	Thr	Ala	Thr	Ala	Leu 390		Glu	Ser	Pro	Leu 395		Ala	Thr	Val	G1u 400	
	Ala	Leu	Gln	Ser 405		Leu	Lys		G1u 410		Leu	Gln	Pro	Gly 415		
Ser	Lys	Ala	Gly 420		Val	Tyr	Ile			Cys	Tyr	Arg	G1u 430		Gly	
Lys	Asn	Ser 435		Ala	Arg	Trp	Trp 440		Lys	Leu	Ala	Leu 445		Leu	Pro	
Asp	Val 450		Lys	Glu	Asp	Leu 455		He	Gln	Lys	Asp 460		Glu	Glu	Leu	
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	gtc Val 20						cag Gln	96
	ctc Leu							144
	aga Arg							192
	tgg Trp							240
	aag Lys							288
	att Ile 100							336
	ggg Gly							384
	atc Ile							432
	tgg Trp							480
	gac Asp							528
	ttc Phe 180							576

							ctg Leu				624
							aat Asn 220				672
							gaa Glu				720
							gat Asp				768
							gac Asp				816
			-	 -	-	_	ttt Phe	_	~ ~		864
							gtg Val 300				912
							tcg Ser				960
							agc Ser				1008
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							ggc Gly				1104

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Arg	Ile	Pro	Leu 260	Glu	Asp	Ile	Pro	G1u 265	Asp	Asp	Asp	Glu	Cys 270	Ser	Ala	
Trp	Leu	His 275	Lys	Leu	Tyr	Gln	G1u 280	Lys	Asp	Ala	Phe	G1n 285	G1u	Glu	Tyr	
Tyr	Arg 290	Thr	Gly	Thr	Phe	Pro 295	Glu	Thr	Pro	Met	Val 300	Pro	Pro	Arg	Arg	
Pro 305	Trp	Thr	Leu	Val	Asn 310	Trp	Leu	Phe	Trp	Ala 315	Ser	Leu	Val	Leu	Tyr 320	
Pro	Phe	Phe	Gln	Phe 325	Leu	Val	Ser	Met	11e 330	Arg	Ser	Gly	Ser	Ser 335	Leu	
Thr	Leu	Ala	Ser 340	Phe	Пе	Leu	Val	Phe 345	Phe	Val	Ala	Ser	Va1 350	Gly	Val	
Arg	Trp	Met 355	He	Gly	Val	Thr	G1u 360	He	Asp	Lys	Gly	Ser 365	Ala	Tyr	Gly	
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				gcg Ala												96
				tgg Trp			-			_	-	-				144
				ccc Pro		_					_	_	-	-		192
ССС	agc	aac	acc	cct	gcc	acg	ccg	ССС	aac	ttc	ССС	gat	gcg	ctg	gcc	240

Pro 65	Ser	Asn	Thr	Pro	Ala 70	Thr	Pro	Pro	Asn	Phe 75	Pro	Asp	Ala	Leu	Ala 80		
														aac Asn 95	-		288
										-			-	ccc Pro		(336
									-				-	ccc Pro			384
									_		-		-	tgg Trp			432
		_	_	-			-	-	•		_	•	~ ~	gcc Ala	_	,	480
_	ggc Gly	-	-	tga *													495
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Phe	Val	Leu	Ala 20		Gly	Cys	Ala	A1 a 25		Gln	Ala	Lys	G1n 30	Leu	Leu		
Gln	Ala	A1a 35		Trp	Gln	Phe	Glu 40		Ala	Leu	Ser	Thr 45		Phe	G1n		
Glu	Thr 50		Пе	Pro	Asn	Ser 55	_	His	His	His	G1n 60		Met	Cys	Thr		
Pro		Asn	Thr	Pro	Ala		Pro	Pro	Asn	Phe		Asp	Ala	Leu	Ala		

Met	Phe	Ser	Lys	Leu 85	Arg	Ala	Ser	Glu	Gly 90	Leu	Gln	Ser	Ser	Asn 95	Ser	-
Pro	Met	Thr	Ala 100	Ala	Ala	Cys	Ser	Pro 105	Pro	Ala	Asn	Phe	Ser 110	Pro	Phe	
Trp	Ala	Ser 115	Ser	Pro	Pro	Ser	His 120	Gln	Ala	Pro	Trp	11e 125	Pro	Pro	Ser	
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													ctg Leu 30			96
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													gat Asp			192
													aaa Lys			240
aaa	ggc	aaa	ggt	aaa	aaa	cat	gaa	gca	gat	gag	ttg	agt	gga	gat	gct	288

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Lys	Gly	Lys	Gly	Lys 85	Lys	His	Glu	Ala	Asp 90	Glu	Leu	Ser	Gly	Asp 95	Ala	
			gat Asp 100													336
			gag Glu													384
			aat Asn													432
			aac Asn					_				_	-			480
			gaa Glu													528
			gat Asp 180													576
			aaa Lys													624
			ctt Leu													672
			gag G1u													720
			tcg Ser						-	-	_					768
ttt	gat	ggt	gat	gac	ctc	cta	gaa	aca	ggt	aaa	aat	gtg	aaa	att	aca	816

Phe	Asp	Gly	Asp 260	Asp	Leu	Leu	Glu	Thr 265	Gly	Lys	Asn	Val	Lys 270	Пе	Thr	
					aag Lys											864
					agc Ser											912
					gac Asp 310											960
					aag Lys										gat Asp	1008
					ccc Pro										aag. Lys	1056
				-	tct Ser		_	-	_					-	_	1104
					agt Ser					-		-				1152
			-	-	gga G1y 390							_		-	_	1200
					aaa Lys											1248
					cct Pro		_		_				-		_	1296
tct	tca	agc	aca	gag	gtg	tcc	agg	tgt	att	gca	cat	ctt	cat	cgc	act	1344

Ser	Ser	Ser 435	Thr	Glu	Val	Ser	Arg 440	Cys	He	Ala	His	Leu 445	His	Arg	Thr	
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	-	aaa Lys	-	_	_		•		•	•	_	•	-		_	1440
		gga Gly	-				_		-	_	_	_	_			1488
_		gtc Val			-			_	_					•		1536
		agc Ser 515				_			-			-		_		1584
gat	aat	gga	aca	ant	aac	~~~	202	tca	a22	+00	-++	222				1622
-		Gly		-					-	_				_	-	1632
Asp	Asn 530 aag		Ala cga	Ser	Gly	Gln 535 tcc	Thr aag	Ser agt	Glu cca	Ser gga	Ile 540 cat	Lys atg	Lys gta	Ser	Glu cta	1680
gaa Glu 545 gac	Asn 530 aag Lys caa	Gly aag	Ala cga Arg	Ser ata Ile	Gly agt Ser 550 gat	Gln 535 tcc Ser	Thr aag Lys	Ser agt Ser	Glu cca Pro	Ser gga Gly 555 tca	Ile 540 cat His	Lys atg Met	Lys gta Val	Ser ata Ile	Glu cta Leu 560 tat	
gaa Glu 545 gac Asp	Asn 530 aag Lys caa Gln	Gly aag Lys	cga Arg aaa Lys	ser ata Ile gga Gly 565	agt Ser 550 gat Asp	Gln 535 tcc Ser cat His	Thr aag Lys tgt Cys aag	ser agt ser aga Arg	Glu cca Pro cca Pro 570	gga Gly 555 tca Ser	Ile 540 cat His aga Arg	Lys atg Met aga Arg	Lys gta Val gga Gly	ser ata Ile aga Arg 575 cta	cta Leu 560 tat Tyr	1680
gaa Glu 545 gac Asp Glu	Asn 530 aag Lys caa Gln aaa Lys	aag Lys act Thr	cga Arg aaa Lys cat His 580 gat	Ser ata Ile gga Gly 565 gga Gly	agt Ser 550 gat Asp aga Arg	Gln 535 tcc Ser cat His agt Ser	Thr aag Lys tgt Cys aag Lys	agt Ser aga Arg gaa Glu 585	Glu cca Pro cca Pro 570 aag Lys	gga Gly 555 tca Ser gag Glu	Ile 540 cat His aga Arg aga Arg	Lys atg Met aga Arg gct Ala	gta Val gga Gly agt Ser 590	ser ata Ile aga Arg 575 cta Leu	cta Leu 560 tat Tyr	1680 1728

PCT/US00/29052

Lys	Met 610	Lys	Glu	Gln	Arg	Leu 615	Arg	Glu	His	Leu	Va1 620	Arg	Phe	Glu	Arg	
	cga Arg									-			-		-	1920
	cgt Arg										_	_		_	_	1968
	gaa Glu	-					-		_		-		_			2016
	cta Leu	-	_		_	-	-	-	_	-	-	-		_	•	2064
	cgt Arg 690															2112
	aga Arg															2160
	aaa Lys															2208
	gat Asp												-		-	2256
	cga Arg															2304
	gac Asp 770												_		•	2352
gta	cag	tct	tca	tct	ttt	gaa	agg	cgg	gat	cgc	ttt	gtt	ggt	caa	agt	2400

Va1 785	Gln	Ser	Ser	Ser	Phe 790	Glu	Arg	Arg	Asp	Arg 795 •	Phe	Val	Gly	Gln	Ser 800	
				-	cga Arg			-	•		•	-		•		2448
-	_				aat Asn		_	-		_	•		~ ~			2496
		-		-	ctt Leu	_	_		-		-	-	_	-		2544
-	-	-	-		aga Arg	_					_			-		2592
					cct Pro 870											2640
	_			-	gaa Glu		_	-			-			_		2688
					gaa Glu	_			_	-	-				•	2736
					cct Pro											2784
					aga Arg											2832
-					gag Glu 950	_			-	-	_				=	2880
aca	agc	gga	cca	agg	aaa	gag	tgg	cat	ggt	cca	ссс	tct	caa	999	cct	2928

Thr	Ser	Gly	Pro	Arg 965	Lys	Glu	Trp	His	G1y 970	Pro	Pro	Ser	Gln	Gly 975	Pro	
											cgg Arg					2976
			Gln			-		Ala			att Ile		Arg		_	3024
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	Phe	-				Pro	•	-	ttc Phe	tga *						3105
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WO 01/29221 PCT/US00/29052

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		 _				ttt Phe			J - J	 624
						ttg Leu 220				672
	_	_		_		tat Tyr		•		720
						att Ile				768
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						ttc Phe				864
						atc Ile 300				912
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1,00	130	πор	LCU	LCU	um	135	uij	110	пор	• • • •	140	110	JCI	· IIC	LCu
Asn		Val	Len	Asn	Gln		Asn	Tro	Ala	Phe		Glu	Phe	Πρ	Glv
145	00.			, 1311	150	LCU	71311		, u	155	501	dia	1110	110	160
	He	Gln	Glu	He	Gln	GIn	Ala	Ala	Glu		leu	Glu	Ara	Asn	
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Val	Asp	Ser	Ara		Leu	Lvs	Val	Cvs		Thr	Cvs	Phe	Asp		Ser
			180			-5 -		185			- J		190	LCu	.
Val	Ser	Leu		Arq	Val	Leu	Glu	Met	Thr	He	Thr	Leu		Pro	Glu
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Leu	Ala	Gln	Leu	Leu	Asn	Gln	Val	Leu	Asn	Arg	Val	Thr	Ala	Glu	Arg
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Leu		Ala	Asp	Pro	Cys		Gln	Leu	Arg	Ser		Cys	Tyr	Leu	Leu
0.7	290	_		_	_	295	_				300	_	_		
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Arg	Lys	Arg	Pne		Leu	Gin	Ser	lyr		Asp	lyr	He	Ser		Asp
C1	Lau	41.	C1	325	C1	C1	Mat	1	330	112 -		TL -	.	335	_
GIU	Leu	Ald	340	VdI	Glu	GIN	met		Ala	HTS	Leu	Inr		АТа	Ser
۸1 s	GIn.	۸1 ء		۸۱۰	Λla	con	Lou	345	The	Can	C1	C1	350	۰	43.
Ala	din	355	Ald	Ald	Ala	3ei	360	PIO	1111	ser.	GIU		ASP	ser.	Ald
Pro	Ser		Mot	Pro	Thr	Dro		Lau	Lou	Cvc	San	365 Son	Dro	Val	۸٦٥
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Thr		Pro	Δla	lvs	Pro		Ser	Thr	Sar	Thr	500				
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65					70					75					80	
	oot	000		+-+			.+									000
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Lys	110	110	um	85	uly	um	Add	uiu	90	Lys	1112	116	Ald	95	Ald	
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									aga Arg		1008

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Vai	Leu 50	Gin	Lys	Ala	He	tys 55	vai	Gly	Pro	Glu	Asn 60	Met	GIn	He	Met
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		195			Trp		200					205			
	210				He	215		-			220				
225					11e 230					235					240
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Lys	Arg	Ser	Gln	Asp 325	Val	Leu	His	Arg	Tyr 330	He	Glu	Asp	Glu	Arg 335	Leu
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Pro	G1u 370	Asn	Val	Asp	Gly	Asn 375		Trp	Ala	G1n	Va1 380		Ala	Leu	Tyr
Pro 385	Thr	Leu	Val	Glu	Cys 390	He	Thr	Cys	Ser	Ser 395		Glu	Val	Cys	Ser 400

Ala	Leu	Lys	Glu	A1a 405	Leu	Val	Pro	Phe	Lys 410	Asp	Phe	Met	Gln	Pro 415	Pro	
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											gct Ala					528
							_		_		cag Gln	-	-	_	_	576
			-								ctt Leu		_	•	_	624
								_			cat His 220			_		672
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											gtg Val					816
											gct Ala					864
aca	ggt	gag	atg	tcc	cat	cat	gat	act	ttg	gat	gct	gct	tcc	caa	gga	912

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Ser	Phe	Ala	G1u 20	Ser	Trp	Asp	Asn	Va1 25	Gly	Leu	Leu	Val	Glu 30	Pro	Ser	
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Glu	Va1 50	Met	Glu	Glu	Val	Leu 55	Gln	Lys	Lys	Ala	Asp 60	Leu	He	Leu	Ser	
Tyr 65	His	Pro	Pro		Phe 70	_	Pro	Met	Lys	Arg 75	He	Thr	Trp	Asn	Thr 80	
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	G1y 290					295		•		·	300					
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	His								cag G1n				336
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									gat Asp 205				624
									gtc Val				672

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	ccc Pro 50					_	_				_		•			192
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	gcc Ala		•	-	_	-	_		_	•		•			•	288
	aag Lys															336
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Arg Pro Asn Thr Ser Pro Asp Arg Gly Ser Arg Asp Arg Lys Ser Gly
Gly Arg Leu Gly Ser Pro Lys Pro Glu Arg Gln Arg Gly Gln Asn Ser
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Lys Ala Pro Ala Ala Pro Ala Asp Arg Lys Arg Xaa Xaa Ser Pro Gln
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Pro Gly Ala Ala Ser Thr Lys Ser Gly Lys Ala Ser Thr Leu Ser Arg
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gca Ala												336
atg Met												38 4
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gat Asp												528
tcc Ser												576
gca Ala												624

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-				-	agt Ser			_	-					•	768
					gca Ala		_	_		_		_			816
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Met Cys Leu Leu Ala Val Ser Pro Asp Gly Asn Trp Leu Ala Ala Ser

1 5 10 15

ggt acc agt gct gga gtc cat gtc tac aac gta aaa cag cta aag ctt 96 Gly Thr Ser Ala Gly Val His Val Tyr Asn Val Lys Gln Leu Lys Leu 20 25 30

	_											-	_	gct Ala			144
_							-		-		_	•	•	cag G1n	_		192
														cgg Arg		;	240
-	_	_	_										_	act Thr 95		:	288
				_				_	-	_	_			ctt Leu		;	336
		-		_		_			_	_		•		ctt Leu		(;	384
	_											_		gac Asp			432
	-	-			cca Pro .150				_	_				acc Thr	taa *	•	480
	.,	310.	250														

<210> 258

<211> 159

<212> PRT

<213> Homo sapiens

<400> 258

Met Cys Leu Leu Ala Val Ser Pro Asp Gly Asn Trp Leu Ala Ala Ser 1 5 5 10 15 15 Gly Thr Ser Ala Gly Val His Val Tyr Asn Val Lys Gln Leu Lys Leu 20 25 30

His	Cys	Thr 35	Val	Pro	Ala	Tyr	Asn 40	Phe	Pro	Val	Thr	A1a 45	Met	Ala	He		
Ala	Pro 50		Thr	Asn	Asn	Leu 55	Val	He	Ala	His	Ser 60	Asp	Gln	Gln	Val		
Phe 65	Glu	Tyr	Ser	He	Pro 70	Asp	Lys	Gln	Tyr	Thr 75	Asp	Trp	Ser	Arg	Thr 80		
Val	Gln	Lys	Gln	G1y 85	Phe	His	His	Leu	Trp 90	Leu	Gln	Arg	Asp	Thr 95			
Ile	Thr	His	Ile 100	Ser	Phe	His	Pro	Lys 105	Arg	Pro	Met	His	Ile 110	Leu	Leu		
His	Asp	Ala 115	Tyr	Met	Phe	Cys	11e 120	He	Asp	Lys	Ser	Leu 125	Pro	Leu	Pro		
Asn	Asp 130	Lys	Thr	Leu	Leu	Tyr 135	Asn	Pro	Phe	Pro	Pro 140	Thr	Asn	Asp	He		
11e 145	Ala	Gln	Leu	Pro	Pro 150	Pro	He	Lys	Lys	Lys 155	Lys	Phe	Gly	Thr			
	<2 <2			sat	oiens	5											
	<2	220> 221> 222>	CDS	(6	527)												
ato		100>	259 tct	tta	ctt	aca	aac	gag	cas	tta	ata	cat	act	tta	aac	Л	8
			Ser													4	O
			gag Glu 20									-	-		-	9	6
			gcc Ala													14	4
_			caa Gln		-	-			_				_	_		19	2
cag	cat	ctg	aga	gaa	agg	gat	tcc	866	cta	tac	ctc	cat	gag	ctc	cta	24	0

G1n 65	His	Leu	Arg	Glu	Arg 70	Asp	Ser	Lys	Leu	Tyr 75	Leu	His	Glu	Leu	Leu 80	
						ctc Leu										288
						ctg Leu										336
						acc Thr									_	384
						gac Asp 135	_		-			_		. •	_	432
						ttc Phe										480
						gga Gly	_						_	_	•	528
						ttg Leu										576
						cgg Arg										624
taa																627

<210> 260

<211> 208

<212> PRT

<213> Homo sapiens .

<400> 260 Met Ala Ser Ser Leu Leu Ala Gly Glu Arg Leu Val Arg Ala Leu Gly Pro Gly Gly Glu Leu Glu Pro Glu Arg Leu Pro Arg Lys Leu Arg Ala Glu Leu Glu Ala Ala Leu Gly Lys Lys His Lys Gly Gly Asp Ser Ser 40 Ser Gly Pro Gln Arg Leu Val Ser Phe Arg Leu Ile Arg Asp Leu His 55 Gln His Leu Arg Glu Arg Asp Ser Lys Leu Tyr Leu His Glu Leu Leu Glu Gly Ser Glu Ile Tyr Leu Pro Glu Val Val Lys Pro Pro Arg Asn 90 Pro Glu Leu Val Ala Arg Leu Glu Lys Ile Lys Ile Gln Leu Ala Asn 105 Glu Glu Tyr Lys Arg Ile Thr Arg Asn Val Thr Cys Gln Asp Thr Arg 120 125 His Gly Gly Thr Leu Ser Asp Leu Gly Lys Gln Val Arg Ser Leu Lys 135 Ala Leu Val Ile Thr Ile Phe Asn Phe Ile Val Thr Val Val Ala Ala 145 150 155 160 Phe Val Cys Thr Tyr Leu Gly Ser Gln Tyr Ile Phe Thr Glu Met Ala 170 Ser Arg Val Leu Ala Ala Leu Ile Val Ala Ser Val Val Gly Leu Ala 180 185 Glu Leu Tyr Val Met Val Arg Ala Met Glu Gly Glu Leu Gly Glu Leu 195 200 205 <210> 261 <211> 1092 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(1092) <400> 261 atg gcc gca gcg gcg atg gcg gca gcg gca ggt gga ggg gct ggc gcg 48 Met Ala Ala Ala Met Ala Ala Ala Ala Gly Gly Gly Ala Gly Ala 1 5 ged ege tee etc teg ege tte ega gge tge etg get gge geg etg etc 96

Ala	Arg	Ser	Leu 20	Ser	Arg	Phe	Arg	G1y 25	Cys	Leu	Ala	Gly	A1a 30	Leu	Leu	
	gac Asp		-								-		-	-	_	144
	tca Ser 50	-		-		_	_	_	-		_	-			_	192
	ggg Gly	-				-	-	_				-	-		-	240
	gcc Ala					_		_		_	-		-		•	288
	gtg Val								_			_		_		336
	agg Arg									-		_	-		-	384
	ccc Pro 130					-				-		-	-			432
	aaa Lys								-	_			-			480
	ctg Leu	-		-	_		-	-		_	-		-			528
	gcc Ala								_					-		576
ctg	cag	gcc	ctg	gct	gtg	cac	ctg	gcc	ttg	cag	ggc	gag	tct	tcc	agc	624

Leu	Gln	Ala 195	Leu	Ala	Val	His	Leu 200	Ala	Leu	Gln	Gly	G1u 205	Ser	Ser	Ser	
				_			_			-		-	-	gag Glu	~ ~	672
														gag Glu		720
			-	_	_	_	-						•	cag Gln 255	_	768
					-									att Ile	-	816
														tgc Cys		864
								-			_			agg Arg		912
														gcc Ala		960
														gtg Val 335		1008
														atc Ile		1056
-		-	_		cgt Arg	-		_	_	•	tga *					1092

<210> 262

<211> 363 <212> PRT <213> Homo sapiens <400> 262 Met Ala Ala Ala Met Ala Ala Ala Ala Gly Gly Gly Ala Gly Ala Ala Arg Ser Leu Ser Arg Phe Arg Gly Cys Leu Ala Gly Ala Leu Leu Gly Asp Cys Val Gly Ser Phe Tyr Glu Ala His Asp Thr Val Asp Leu 40 Thr Ser Val Leu Arg His Val Gln Ser Leu Glu Pro Asp Pro Gly Thr Pro Gly Ser Glu Arg Thr Glu Ala Leu Tyr Tyr Thr Asp Asp Thr Ala Met Ala Arg Ala Leu Val Gln Ser Leu Leu Ala Lys Glu Ala Phe Asp 90 Glu Val Asp Met Ala His Arg Phe Ala Gln Glu Tyr Lys Lys Asp Pro 100 105 Asp Arg Gly Tyr Gly Ala Gly Val Val Thr Val Phe Lys Lys Leu Leu 115 120 Asn Pro Lys Cys Arg Asp Val Phe Glu Pro Ala Arg Ala Gln Phe Asn 135 140 Gly Lys Gly Ser Tyr Gly Asn Gly Gly Ala Met Arg Val Ala Gly Ile 150 155 Ser Leu Ala Tyr Ser Ser Val Gln Asp Val Gln Lys Phe Ala Arg Leu 165 170 Ser Ala Gln Leu Thr His Ala Ser Ser Leu Gly Tyr Asn Gly Ala Ile 185 Leu Gln Ala Leu Ala Val His Leu Ala Leu Gln Gly Glu Ser Ser 200 Glu His Phe Leu Lys Gln Leu Leu Gly His Met Glu Asp Leu Glu Gly 215 220 Asp Ala Gln Ser Val Leu Asp Ala Arg Glu Leu Gly Met Glu Glu Arg 225 230 235 Pro Tyr Ser Ser Arg Leu Lys Lys Ile Gly Glu Leu Leu Asp Gln Ala 250 Ser Val Thr Arg Glu Glu Val Val Ser Glu Leu Gly Asn Gly Ile Ala 260 265 Ala Phe Glu Ser Val Pro Thr Ala Ile Tyr Cys Phe Leu Arg Cys Met 275 280 285 Glu Pro Asp Pro Glu Ile Pro Ser Ala Phe Asn Ser Leu Gln Arg Thr 290 295 300

Leu 305	Пe	Tyr	Ser	Ile	Ser 310	Leu	Gly	Gly	Asp	Thr 315	Asp	Thr	Пe	Ala	Thr 320	
	Ala	Gly	Ala	11e 325		Gly	Ala	Tyr	Tyr 330		Met	Asp	Gln	Val 335		
Glu	Ser	Trp	G1n 340	Gln	Ser	Cys	Glu	Gly 345	Tyr	Glu	Glu	Thr	Asp 350		Leu	
Ala	Gln	Ser 355	Leu	His	Arg	Val	Phe 360	Gln	Lys	Ser						
	<2 <2	212>	1239 DNA		oiens	5										
	<	220> 221> 222>		(1239))										
		100>														
	gcc Ala															48
	cat His															96
	aga Arg				-			_	_	_			-	_	_	144
tcg Ser	tta Leu 50	gga Gly	agc Ser	agc Ser	agg Arg	gtc Val 55	cct Pro	cgg Arg	tgt Cys	999 Gly	caa G1n 60	ggg Gly	act Thr	ctg Leu	ctg Leu	192
	cag Gln															240
	tgc Cys															288
cga	999	gag	cta	cag	cga	gtc	cca	acc	ctg	cta	ctg	ССС	atg	cct	acg	336

Arg	Gly	Glu	Leu 100	Gln	Arg	Val	Pro	Thr 105	Leu	Leu	Leu	Pro	Met 110	Pro	Thr	
	_	-		ccc Pro		-				_		•				384
				tca Ser					-					-		432
				atg Met												480
				gct Ala 165												528
				gtg Val		-			-		_					576
				ctg Leu		_	_			-	_		_	_		624
				aac Asn										-	-	672
				ctc Leu												720
				cac His 245												768
				gtc Val												816
gga	gcc	ttg	cga	gct	ctg	agc	ctg	cct	ctg	acc	cag	ttg	cct	gtg	tcc	864

G	ly	Ala	Leu 275	Arg	Ala	Leu	Ser	Leu 280	Pro	Leu	Thr	Gln	Leu 285	Pro	Val	Ser	
	-		_					cct Pro	-	-		_	-			_	912
L						_	-	act Thr				-		_		_	960
					-		-	gtg Val	-		_		-				1008
								gat Asp									1056
	_	_	_				-	ctg Leu 360	-	•							1104
		_			_			aat Asn		_						-	1152
L				_	-			ctg Leu	_	-				-	_	_	1200
								999 Gly	•				tag *				1239

<210> 264

<211> 412

<212> PRT

<213> Homo sapiens

<400> 264

Met Ala Leu Ala Leu Leu Ser Arg Leu Leu Pro Gly Ser Glu Tyr Leu $1 \ 5 \ 10 \ 15$

His	Glu	Leu 20	Leu	Leu	Ser	Cys	Va1 25	Phe	Arg	Leu	Glu	Phe 30	Leu	Pro
Arg	Thr 35	Ser	Gly	Gly	Pro	G1u 40	Ala	Ala	Asp	Phe	Ser 45	Asp	Gln	Leu
Leu 50	Gly	Ser	Ser	Arg	Va1 55	Pro	Arg	Cys	Gly	G1n 60	Gly	Thr	Leu	Leu
Gln	Ala	Cys	Gln	Asp 70	Leu	Pro	Ser	He	Arg 75	Asn	Cys	Tyr	Leu	Thr 80
Cys	Ser	Pro	A1a 85	Arg	Ala	Ser	Leu	Leu 90	Ala	Ser	Gln	Ala	Leu 95	His
Gly	Glu	Leu 100	Gln	Arg	Val	Pro	Thr 105	Leu	Leu	Leu	Pro	Met 110	Pro	Thr
Pro	Leu 115	Leu	Pro	Thr	Asp	Trp 120	Pro	Phe	Leu	Pro	Leu 125	Ile	Arg	Leu
His 130	Arg	Ala	Ser	Asp	Thr 135	Pro	Ser	Gly	Leu	Ser 140	Pro	Thr	Asp	Thr
Gly	Thr	Ala	Met	Arg 150	Val	Leu	Gln	Trp	Val 155	Leu	Val	Leu	Glu	Ser 160
Arg	Pro	Gln	Ala 165	Leu	Trp	Ala	Val	Pro 170	Pro	Ala	Ala	Arg	Leu 175	Ala
Leu	Met	Cys 180	Val	Phe	Leu	Val	Asp 185	Ser	Glu	Leu	Phe	Arg 190	Glu	Ser
Val	G1n 195	His	Leu	Val	Ala	A1a 200	Leu	Leu	Ala	Gln	Leu 205	Cys	Gln	Pro
Va1 210	Leu	Pro	Asn	Leu	Asn 215	Leu	Asp	Cys	Arg	Leu 220	Pro	Gly	Leu	Thr
Phe	Pro	Asp	Leu	Tyr 230	Ala	Asn	Phe	Leu	Asp 235	His	Phe	Glu	Ala	Val 240
Phe	Gly	Asp	His 245	Leu	Phe	Gly	Ala	Leu 250	Val	Leu	Leu	Pro	Leu 255	Gln
Arg	Phe	Ser 260	Val	Thr	Leu	Arg	Leu 265	Ala	Leu	Phe	Gly	G1u 270	His	۷a۱
Ala	Leu 275	Arg	Ala	Leu	Ser	Leu 280	Pro	Leu	Thr	Gln	Leu 285	Pro	Val	Ser
G1u 290	Cys	Tyr	Thr	Val	Pro 295	Pro	Glu	Asp	Asn	Leu 300	Ala	Leu	Leu	Gln
Tyr	Phe	Arg	Thr	Leu 310	Val	Thr	Gly	Ala	Leu 315	Arg	Pro	Arg	Trp	Cys 320
Val	Leu	Tyr	Ala 325	Val	Ala	Val	Ala	His 330	Val	Asn	Ser	Phe	I le 335	Phe
Gln	Asp	Pro 340	Gln	Ser	Ser	Asp	G1u 345	Val	Lys	Ala	Ala	Arg 350		Ser
Leu	G1n 355	Lys	Thr	Trp	Leu	Leu 360	Ala	Asp	Glu	Gly	Leu 365	Arg	Gln	His
	Arg Leu 50 Gln Cys Gly Pro His 130 Gly Arg Leu Val 210 Phe Arg Ala Glu 290 Tyr Val Gln	Arg Thr 35 Leu Gly 50 Gln Ala Cys Ser Gly Glu Pro Leu Het 115 His Arg 130 Gly Thr Arg Pro Leu Met Val Gln 195 Val Leu 210 Phe Pro Phe Gly Arg Phe Ala Leu 275 Glu Cys 290 Tyr Phe Val Leu Gln Asp Leu Gln Asp Leu Gln Asp	Arg Thr Ser 35 Leu Gly Ser 50 Gln Ala Cys Cys Ser Pro Gly Glu Leu 100 Pro Leu Leu 115 His Arg Ala 130 Gly Thr Ala Arg Pro Gln Leu Met Cys 180 Val Gln His 195 Val Leu Pro 210 Phe Pro Asp Phe Gly Asp Arg Phe Ser 260 Ala Leu Arg 275 Glu Cys Tyr 290 Tyr Phe Arg Val Leu Tyr Gln Asp Pro 340 Leu Gln Lys	Arg Thr Ser Gly 35 Leu Gly Ser Ser 50 Gln Ala Cys Gln Cys Ser Pro Ala 85 Gly Glu Leu Gln 100 Pro Leu Leu Pro 115 His Arg Ala Ser 130 Gly Thr Ala Met Arg Pro Gln Ala 165 Leu Met Cys Val 180 Val Gln His Leu 195 Val Leu Pro Asn 210 Phe Pro Asp Leu Phe Gly Asp His 245 Arg Phe Ser Val 260 Ala Leu Arg Ala 275 Glu Cys Tyr Thr 290 Tyr Phe Arg Thr Val Leu Tyr Ala 325 Gln Asp Pro Gln 340 Leu Gln Lys Thr	Arg Thr Ser Gly Gly 35 Leu Gly Ser Ser Arg 50 Gln Ala Cys Gln Asp 70 Cys Ser Pro Ala Arg 85 Gly Glu Leu Gln Arg 100 Pro Leu Leu Pro Thr 115 His Arg Ala Ser Asp 130 Gly Thr Ala Met Arg 150 Arg Pro Gln Ala Leu 165 Leu Met Cys Val Phe 180 Val Gln His Leu Val 195 Val Leu Pro Asn Leu 210 Phe Pro Asp Leu Tyr 230 Phe Gly Asp His Leu 210 Phe Pro Asp Leu Tyr 230 Phe Gly Asp His Leu 245 Arg Phe Ser Val Thr 260 Ala Leu Arg Ala Leu 275 Glu Cys Tyr Thr Val 290 Tyr Phe Arg Thr Leu 310 Val Leu Tyr Ala Val 325 Gln Asp Pro Gln Ser 340 Leu Gln Lys Thr Trp	Arg Thr Ser Gly Gly Pro 35 Leu Gly Ser Ser Arg Val 50 Gln Ala Cys Gln Asp Leu 70 Cys Ser Pro Ala Arg Ala 85 Gly Glu Leu Gln Arg Val 100 Pro Leu Leu Pro Thr Asp 115 His Arg Ala Ser Asp Thr 130 Arg Pro Gln Ala Leu Trp 165 Leu Met Cys Val Phe Leu 180 Val Gln His Leu Val Ala 195 Val Leu Pro Asn Leu Asn 210 Phe Pro Asp Leu Tyr Ala 230 Phe Gly Asp His Leu Phe 245 Arg Phe Ser Val Thr Leu 260 Ala Leu Arg Ala Leu Ser 275 Glu Cys Tyr Thr Val Pro 290 Tyr Phe Arg Thr Leu Val Ala 310 Val Leu Tyr Ala 295 Tyr Phe Arg Thr Leu Val Ala 325 Gln Asp Pro Gln Ser Ser 340 Leu Gln Lys Thr Trp Leu Ceu Gln Ser Ser 340 Leu Gln Lys Thr Trp Leu Ceu Ceu Gln Ser Ser 340 Leu Gln Lys Thr Trp Leu Ceu Ceu Gln Ser Ser 340 Leu Gln Lys Thr Trp Leu Ceu Ceu Gln Ser Ser 340 Leu Gln Lys Thr Trp Leu Ceu Ceu Ceu Ceu Ceu Ceu Ceu Ceu Ceu C	Ser Gly Gly Pro Glu A0 A0 A0 A0 A0 A0 A0 A	20	Ser Ser	Ser Gly Gly Pro Glu Ala Ala Asp Asp	Secondary Seco	Second	Second Process	Arg Thr Ser Gly Gly Pro Glu Ala Asp Phe Ser Asp Gln Asp Ho 45 Asp Gln Asp Leu Glo Asp Cys Gln Gln Gln Gln Leu Cys Gln Gln Asp Leu Pro Ser Ilee Asp Asp Leu Pro Asp Asp Asp Asp Fro Asp Asp Asp Asp Asp Fro Asp Asp<

Leu	Leu 370	His	Tyr	Lys	Leu	Pro 375	Asn	Ser	Thr	Leu	Pro 380	Glu	Gly	Phe	Glu	
Leu 385	Tyr	Ser	Gln	Leu	Pro 390	Pro	Leu	Arg	Gln	His 395		Leu	Gln	Arg	Leu 400	
Thr	Ser	Thr	Val	Leu 405	Gln	Asn	Gly	·Val	Ser 410	Glu	Thr					
	<'a	210> 211> 212> 213>	576 Dna	o saj	oiens	5										
	<'	220> 221> 222>	CDS (1)	(!	576)											
		400>														
		-	-	-	gaa Glu	-	-	-	-				-		_	48
					gcc Ala											96
					cac His											144
					ttc Phe											192
					gga Gly 70											240
					ctg Leu											288
					agg Arg											336

											gcc Ala					3	384
											gtg Val 140					4	132
					-					-	gct Ala		_		-		180
										-	cag G1n			_	-	į	528
											cgg Arg				tga *	Ę	576
	<2 <2	210> 211> 212> 213>	191 PRT	o saț	oiens	5											
		<001															
Met 1	Ala	Gly	Ala	Ala 5	Glu	Asp	Ala	Arg	Ala 10	Leu	Phe	Arg	Ala	Gly 15	Val		
Cys	Ala	Ala	Leu 20	Glu	Ala	Trp	Pro	A1a 25	Leu	Gln	He	Ala	Va1 30	Glu	Asn		
Gly	Phe	G1y 35	Gly	Val	His	Ser	G1n 40	Glu	Lys	Ala	Lys	Trp 45		Gly	Gly		
Ala	Va1 50		Asp	Tyr	Phe	Met 55	-	Asn	Ala	Asp	Leu 60		Leu	Asp	Glu		
Va1 65		Asp	Phe	Leu	G1 <i>y</i> 70		Leu	Leu	Thr	Asn 75	Glu	Phe	Asp	Thr	Va1 80		
	Glu	Asp	Gly	Ser 85	-	Pro	Gln	Val	Ser 90		Gln	Leu	Gln				
Phe	His	His			Arg	Gly	Asp			Ala	Leu	Arg		95 Met	Ala		
Ser	Cys	He	100 Thr	Gln	Arg	Lys	Cys	105 Lys	Val	Thr	Ala	Thr	110 Ala	Leu	Lys		

Thr	Ala 130	Arg	Glu	Thr	Asp	Glu 135	Asp	Glu	Asp	Asp	Val 140	Asp	Ser	Val	G1u	
Glu 145		Glu	Val	Thr	Ala 150	Thr	Asn	Asp	Gly	Ala 155		Thr	Asp	Gly	Val 160	
Cys	Pro	Gln	Pro	Glu 165	Pro	Ser	Asp	Pro	Asp 170	Ala	Gln	Thr	He	Lys 175	Glu	
Glu	Asp	Пe	Va1 180	Glu	Asp	Gly	Trp	Thr 185	Ile	Val	Arg	Arg	Lys 190	Lys		
	<'a	210> 211> 212> 213>	567 Dna	o sap	oiens	5						-				
	<2	220> 221> 222>		(5	567)											·
		100>														
					gcg Ala											48
				_	cac His			_			_		_			96
					999 Gly											144
					ggt Gly											192
					cct Pro 70											240
					cag G1n											288
ttc	ctc	tcc	aag	act	cgg	gtg	gtc	cag	gag	cac	ggc	999	cgg	gcg	gtg	336

Phe	Leu	Ser	Lys 100	Thr	Arg	Val	Val	Gln 105	Glu	His	Gly	Gly	Arg 110	Ala	Val		-
			gac Asp													3	884
			agt Ser									_			_	4	132
			gac Asp									-				4	180
			gcc Ala													5	528
			ctg Leu 180	-		-					~ ~	tag *					567
	<2 <2	210> 211> 212> 213>	188	sar	oiens	5											
	<4	100>	268														
Met 1	Val	Pro	Gly	Ala 5	Ala	Gly	Trp	Cys	Cys 10	Leu	Val	Leu	Trp	Leu 15	Pro		
Ala	Cys	Val	Ala 20	Ala	His	Gly	Phe	Arg 25	He	His	Asp	Tyr	Leu 30	Tyr	Phe		
Gln	Val	Leu 35	Ser	Pro	Gly	Asp	11e 40	Arg	Tyr	He	Phe	Thr 45	Ala	Thr	Pro		
Ala	Lys 50	Asp	Phe	Gly	Gly	Ile 55	Phe	His	Thr	Arg	Tyr 60	Glu	Gln	He	His		
Leu 65	Val	Pro	Ala	Glu	Pro 70	Pro	Glu	Ala	Cys	G1y 75	Glu	Leu	Ser	Asn	Gly 80		
Phe	Phe	He	Gln	Asp 85	Gln	He	Ala	Leu	Val 90	Glu	Arg	Gly	Gly	Cys 95	Ser		
Phe	Leu	Ser	Lys 100	Thr	Arg	Val	Val	Gln 105	Glu	His	Gly	Gly	Arg 110	Ala	Val		

He	He	Ser 115	Asp	Asn	Ala	Val	Asp 120	Asn	Asp	Ser	Phe	Tyr 125	Val	Glu	Met	
He	Gln 130	Asp	Ser	Thr	Gln	Arg 135	Thr	Ala	Asp	He	Pro 140		Leu	Phe	Leu	
Leu 145	Gly	Arg	Asp	Gly	Tyr 150	Met	Пе	Arg	Arg	Ser 155	Leu	Glu	Gln	His	Gly 160	
Leu	Pro	Trp	Ala	Ile 165	He	Ser	He	Pro	Val 170	Asn	Val	Thr	Ser	I 1e 175	Pro	
Thr	Phe	Glu	Leu 180	Leu	Gln	Pro	Pro	Trp 185	Thr	Phe	Trp					
	<'a	212>	1419 DNA		oiens	5							·			
	<	220> 221> 222>		(1	1419))										
atg		100> ctg		tcg	gcg	ctg	ctg	tgt	gtg	att	gtg	tct	gtt	ctg	acc	48
														Leu 15		
										-			_	cat His		96
											_	_		acg Thr		144
														gag G1u		192
									-	-		-	_	agc Ser		240
-			_				-		-	-				ccg Pro 95	-	288

	-		-	caa Gln					-		_			_	30	36
		_	_	gat Asp	-	_	Glu	_	_					•	38	84
			_	gtg Val				-	-	-		_		_	.43	32
				ata Ile 150	_	-	-	_		-	_	-			48	. 08
_				cag Gln		_				-				•••	52	28
				cac His											57	76
				ttt Phe											62	24
				gcg Ala											67	72
				gtc Val 230											72	20
	_			att Ile	-	_	_		•		_		•	ctt. Leu	7(68
	_		_	ggc Gly			_						_		8:	16

														tat Tyr		864
							_			-				ctt Leu	_	912
														ttc Phe		960
														cat His 335		1008
														aac Asn		1056
														tac Tyr		1104
														999 G1 y		1152
														aca Thr		1200
agt Sen	ggt Gly	tca Ser	gca Ala	ctg Leu 405	agt Ser	cat His	gct Ala	tgc Cys	ttc Phe 410	tgc Cys	tac Tyr	gca Ala	ctg Leu	att Ile 415	tgt Cys	1248
tct Ser	att Ile	cca Pro	gtt Val 420	ttc Phe	acg Thr	tac Tyr	atc Ile	gtt Val 425	ttg Leu	gtg Val	aca Thr	tct Ser	ctg Leu 430	cgt Arg	tat Tyr	1296
														gag Glu		1344

atg cac ctg ctc att aca gct gct gtc tgt gta ttc ttc acg gca atg 1392 Met His Leu Leu Ile Thr Ala Ala Val Cys Val Phe Phe Thr Ala Met 450 455 460 gat caa acc aga ctc aca cag tct tag 1419 Asp Gln Thr Arg Leu Thr Gln Ser * 465 470 <210> 270 <211> 472 <212> PRT <213> Homo sapiens <400> 270 Met Val Leu Ala Ser Ala Leu Leu Cys Val Ile Val Ser Val Leu Thr. 10 Asn Val Leu Val Gly Gly Asn Thr Pro Arg Lys Asn Pro Met His Pro Ser Ser Arg Trp Ser Glu Leu Asp Leu Leu Ile Leu Leu Gly Thr Ala 40 Gly His Val Leu Ser Leu Gly Ala Ser Ser Phe Val Glu Glu Glu His 55 Gln Thr Trp Tyr Phe Leu Val Asn Thr Leu Cys Leu Ala Leu Ser Gln Glu Thr Tyr Arg Asn Tyr Phe Leu Gly Asp Asp Gly Glu Pro Pro Cys 90 Gly Leu Cys Val Glu Gln Gly His Asp Gly Ala Thr Ala Ala Trp Gln Asp Gly Pro Gly Cys Asp Val Leu Glu Arg Asp Lys Gly His Gly Ser 120 Pro Ser Thr Ser Glu Val Leu Arg Gly Arg Glu Lys Trp Met Val Leu 135 140 Ala Ser Pro Trp Leu Ile Leu Ala Cys Cys Arg Leu Leu Arg Ser Leu 150 155 Asn Gln Thr Gly Val Gln Trp Ala His Arg Pro Asp Leu Gly His Trp 170 Leu Thr Ser Ser Asp His Lys Ala Glu Leu Ser Val Leu Ala Ala Leu 180 185 190 Ser Leu Leu Val Val Phe Val Leu Val Gln Arg Gly Cys Ser Pro Val 200 205 Ser Lys Ala Ala Leu Ala Leu Gly Leu Leu Gly Val Tyr Cys Tyr Arg 210 215 220

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		435					440			Lys		445	_		_
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		cag Gln 100					_					336
		tat Tyr										384
		gtg Val										432
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Cla Dan Lau	20 Dha Ara- Cili	. 41- 4	25 Ann. Tour	A DI	30	W. L. T.	
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115	Tyr Gln Leu	120	SEL ASIL	uiii iiis	125	rile diy	
Ser Val Gln 130	Val Tyr Leu	Asn Phe	Gly Val	Phe Tyr 140	Glu Gly	Pro Glu	
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Asp Pro Arg Asp Val Lys Asn Met Asn Thr Trp Leu Leu Phe Leu Pro
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						agt Ser								96
				_		act Thr		_				 _	_	144
						aaa Lys 55								192
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						cat His								288
					-	cag G1n	-	_	_	-	-			336
				-	-	gag G1u	_	_		_		_	~	384
						tta Leu 135								432
						gct Ala								480
						aga Arg								528

												agt Ser			576
								_		_	_	cta Leu	_		624
	-			-	-	-		_	_	-		aat Asn	gta Val	-	672
		_	_	-		_	_	-	_	_	•	aat Asn	_		720
												gca Ala 255			768
												ctc Leu			816
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												aga Arg			912
				tcc Ser		_	_	agg Arg 315	tga *						948

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<211> 315

<212> PRT

<213> Homo sapiens

<400> 284

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	Gly	35					40					45			_
	Thr 50					55					60				
65	Gln				70					75					80
	Pro			85					90					95	
	Leu		100					105					110	·	
	Trp	115					120					125			
	Leu 130					135				•	140				
145					150					155					160
	Asn			165					170				·	175	
	Thr		180					185					190		
	Thr	195					200					205			
	G1u 210					215					220				
225	Thr				230					235	_				240
	Leu			245					250					255	
	Leu		260					265					270		
He	Gln	Va1 275	Thr	Ser	Leu	His	Ala 280	Ala	Leu	Glu	Gln	G1u 285	Arg	Ser	Lys
Val	Lys 290	Val	Leu	G]ú	Ala	G1u 295	Leu	Ala	Lys	Tyr	Gln 300	Gly	Gly	Arg	Lys
Gly 305	Lys	Arg	Asn	Ser	G1u 310	Ser	Asp	Gln	Cys	Arg 315					

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<212> DNA

WO 01/29221 PCT/US00/29052

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	ĞĨy																
_	aag Lys	_	-	-	-		_		-	_	-			-			96
	agc Ser						_	_	_		-	_	_	-		1	44
	gac Asp 50							-				_	_		-	1	92
	gcc Ala															2	40
	tgg Trp												-	-	-	. 2	88
	ctg Leu				_	-						_		-	•	3	36
	atg Met															3	84
	ata Ile 130															4	32
ctt	taa	aan	cat	ana	aat	cta	caa	aat	ata	cta	atc	tta	ato	nat	caa	1	ΩŊ

Leu 145	Trp	Lys	His	Gly	Asn 150	Leu	Arg	Asn	Val	Leu 155	He	Leu	Met	Asp	G1n 160	
														cga Arg 175		528
														cat His		576
														gct Ala		624
														ctg Leu		672
														gtg Val		720
														ttg Leu 255		768
														agg Arg	-	816
														ttc Phe		864
														cgt Arg		912
														tat Tyr		960
gta	tta	gac	cgt	ctc	ctt	gat	cag	gat	cta	cca	agg	gcc	agg	gat	ttc	1008

Val	Leu	Asp	Arg	Leu 325	Leu	Asp	Gln	Asp	Leu 330	Pro	Arg	Ala	Arg	Asp 335	Phe	
	agg Arg							-	-			_	_		_	1056
	atc Ile															1104
	atc Ile 370															1152
	acc Thr				-				-	_	-		_			1200
	ctc Leu															1248
	gag G1u															1296
	cct Pro	_	taa *													1308
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	Lys	Leu	Va1 20	Ser	Cys	Thr	Leu	G1y 25		Lys	Met	Pro	Thr 30		Pro	
Trp	Ser	His 35	Arg	Arg	His	Val	Met 40		Gln	Gly	Glu	G1n 45		Gln	Ile	

Pro	Asp 50	Pro	Cys	Arg	Leu	55 55	Ihr	Ala	Inr	Leu	Lys 60	Cys	Leu	GIn	Ala
G1n 65	Ala	Met	Arg	Glu	G1y 70	Leu	Ala	Lys	Glu	Ser 75	Asp	Glu	Gly	Asp	Asn 80
Leu	Trp	Thr	Leu	Leu 85	Ser	Ser	Pro	Ser	Thr 90	His	His	Пe	Gly	Va1 95	
Ser	Leu	Ala	Arg 100	Ser	Met	Ala	Val	Trp 105		His		Val	Ile 110	Leu	Asp
Ile	Met	Glu 115	Gln	Leu	Leu	Ser	Ser 120	Leu	Thr	Ser	Ser	Ser 125	Glu	Asn	Tyr
Arg	Ile 130	Thr	Gly	Ala	Ala	Phe 135	Phe	Ser	Glu	Leu	Met 140	Lys	Glu	Pro	Пe
Leu 145	Trp	Lys	His	Gly	Asn 150	Leu	Arg	Asn	Val	Leu 155	He	Leu	Met	Asp	Gln 160
Ser	Ala	Trp	Asp	Ser 165	Asn	Ala	Thr	Leu	Arg 170	Gln	Met	Ala	He	Arg 175	Gly
Leu	Gly	Asn	Thr 180	Ala	Ser	Gly	Ala	Pro 185	His	Lys	Val	Lys	Lys 190	His	Lys
G1n	Leu	Met 195	Leu	Glu	Ser	Ile	11e 200	Arg	Gly	Leu	Tyr	His 205	Leu	Ala	Arg
Thr	G1u 210	Val	Val	Cys	Glu	Ser 215	Leu	Lys	Ala	Leu	Lys 220	Lys	Ile	Leu	Glu
225					230					235			Ile		240
Gln	Thr	Arg	Thr	Phe 245	Phe	Glu	Asp	G1u	G1n 250	Asp	Asp	Val	Arg	Leu 255	Thr
Ala	He	Phe	Leu 260	Phe	Glu	Asp		A1 a 265	Pro	Leu	Thr	Gly	Arg 270	Arg	Trp
		275					280			•		285	Ser		
Leu	His 290	Leu	Trp	Asp	Pro	Asn 295	Pro	Lys	He	Gly	Val 300	Ala	Cys	Arg	Asp
Va1 305	Leu	Met	Val	Cys	Ile 310	Pro	Phe	Leu	Gly	Leu 315	Gln	Glu	Leu	Tyr	G1y 320
Val	Leu	Asp.	Arg	Leu 325	Leu	Asp	Gln	Asp	Leu 330	Pro	Arg	Ala	Arg	Asp 335	Phe
Tyr	Arg	Gln	Phe 340	Cys	Val	Lys	Leu	A1a 345	Lys	Lys	Asn	Gln	G1u 350	Пe	Leu
Trp	He	Leu 355	His	Thr	His	Ser	Phe 360	Thr	Phe	Phe	Thr	Ser 365	Thr	Trp	Glu
Val	Ile 370	Arg	Ser	Ala	Ala	Va1 375	Lys	Leu	Thr	Asp	Ala 380		Val	Leu	Asn
Leu 385	Thr	Ser	Gln	Tyr	Va1 390	Glu	Leu	Leu	Asp	Arg 395		Gln	Leu	Thr	Thr 400

Arg	Leu	Gln	Ala	Leu 405	Arg	Gln	Asp	Pro	Cys 410	He	Ser	Val	Gln	Arg 415	Ala	
Ala	Glu	Ala	A1a 420	Leu	G1n	Thr	Leu	Leu 425	Arg	Arg	Cys	Lys	G1u 430		Ser	
He	Pro	Leu 435														
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		212>														
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		220>	000													
		221> 222>	(1).	(8	322)											
		100>														
			gta											-		48
net 1	ASP	Pro	Val	5 5	ыу	ınr	ASP	5er	10	Pro	Leu	АТа	ыу	Leu 15	Ala	
			gcc													96
пр	Ser	ser.	Ala 20	ser.	Ald	Pro	Pro	25	Arg	ыу	rne	ser.	30	rie	ser	
tgc	acc	gtc	gag	999	gca	ССС	gcc	agc	ttt	ggc	aag	agc	ttc	gcg	cag	144
Cys	Thr	Va1 35	Glu	Gly	Ala	Pro	A1a 40	Ser	Phe	Gly	Lys	Ser 45	Phe	Ala	Gln	
			tac													192
Lys	Ser 50	Gly	Tyr	Phe	Leu	Cys 55	Leu	Ser	Ser	Leu	G1y 60	Ser	Leu	Glu	Asn	
ccg	cag	gag	aac	gtg	gtg	gcc	gat	atc	cag	atc	gtg	gtg	gac	aag	agc	240
Pro 65	Gln	Glu	Asn	Val	Va1 70	Ala	Asp	He	Gln	11e 75	Val	Val	Asp	Lys	Ser 80	
ccc	ctg	ccg	ctg	ggc	ttc	tcc	ССС	gtc	tgc	gac	ссс	atg	gat	tcc	aag	288
Pro	Leu	Pro	Leu	G1y 85	Phe	Ser	Pro	Val	Cys 90	Asp	Pro	Met	Asp	Ser 95	Lys	
በርር	tot	ata	tcc	מבב	חבב	ددد	cac	ato	tat	ata	מכב	cta	tta	ccc	ctc	226
			Ser													336
			100	٠	•	•	J	105	- J -		•		110	_		

					gtg Val										384
					ctt Leu 135										432
					aag Lys							_		-	480
					cag Gln								-	_	528
					ctg Leu							_			576
					agg Arg		-					-		•	624
				-	atg Met 215	-		-							672
			-	-	tgc Cys	-		-	-			-			720
					ctg Leu										768
		 		_	acc Thr		-	-	-	-	Pro		_	•	816
tca Ser	_														822

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		220>															
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		100>															
	cca																48
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	agt		_			-				_					•		96
Phe	Ser	Gly	Va 1 20	Glu	Ser	Ala	Leu	Ser 25	Ser	Leu	Lys	Asn	Phe 30	GIn	Ala		
	atc				_	-		-		-	-	-	-	-		1	44
Cys	He	Asn 35	Ser	Gly	Met	Asp	Thr 40	Ala	Ser	Ser	Val	A1 a 45	Leu	Asp	Leu		
						-		-	_		_	_	-	_	gca.	1	192
Val	Glu 50	Ser	Gln	Thr	Glu	Va1 55	Ser	Ser	Glu	Tyr	Ser 60	Met	Asp	Lys	Ala		
atg	gtt	gaa	ttt	gct	aca	ttg	gat	cgg	caa	cta	aac	cat	tat	gta	aag	. 2	240
Met 65	Val	Glu	Phe	Ala	Thr 70	Leu	Asp	Arg	Gln	Leu 75	Asn	His	Tyr	Val	Lys 80		
act	gtt	caa	tct	aca	ata	aat	cat	ata	222	naa	naa	cat	CCA	naa	222	2	288
	Val															2	-00
ata	сса	gat	tta	aaa	tta	ttg	gta	gag	aag	aaa	ttt	ttg	gct	tta	cag	3	336
He	Pro	Asp	Leu 100	Lys	Leu	Leu	Val	Glu 105	Lys	Lys	Phe	Leu	Ala 110	Leu	Gln		
agc	aag	aat	tct	gat	gca	gac	ttt	caa	aat	aat	gaa	aaa	ttt	gta	cag	3	884
Ser	Lys	Asn 115	Ser	Asp	Ala	Asp	Phe 120	Gln	Asn	Asn	Glu	Lys 125	Phe	Val	Gln		
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Phe	Lys 130	Gln	Gln	Leu	Lys	G1u 135	Leu	Lys	Lys	G1n _,	Cys 140	Gly	Leu	Gln	Ala	
_	-	-	_	-		aca Thr	-			-	-	_				480
		_	-			ttc Phe		_				_		-	•	528
_	-					aaa Lys							_		-	576
•		•	•	•		gag Glu				_		_		•	•	624
	_					tgt Cys 215	-		_	-		-	-		•	672
		-	-	_	-	ctt Leu	_		_						•	720
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Cys	Пe	Asn		Gly	Met	Asp	Thr		Ser	Ser	Val	Ala		Asp	Leu	

Val	G1u 50	Ser	Gln	Thr	Glu	Va1 55	Ser	Ser	Glu	Tyr	Ser 60	Met	Asp	Lys	Ala	
Met 65	Val	Glu	Phe	Ala	Thr 70		Asp	Arg	Gln	Leu 75		His	Tyr	Val	Lys 80	
Ala	Val	Gln	Ser	Thr 85	He	Asn	His	Val	Lys 90		Glu	Arg	Pro	Glu 95		
He	Pro	Asp	Leu 100	Lys	Leu	Leu	Val	Glu 105	Lys	Lys	Phe	Leu	Ala 110		Gln	
Ser	Lys	Asn 115		Asp	Ala	Asp	Phe 120		Asn	Asn	Glu	Lys 125		Val	Gln	
Phe	Lys 130	G1n	Gln	Leu	Lys	G1u 135	Leu	Lys	Lys	Gln	Cys 140		Leu	Gln	Ala	
Asp 145	Arg	Glu	Ala	Asp	Gly 150	Thr	Glu	Gly	Val	Asp 155	Glu	Asp	Пe	He	Val 160	
	Gln	Ser	Gln	Thr 165		Phe	Thr	Cys	Pro 170		Thr	Lys	Glu	Glu 175		
Lys	Lys	Pro	Val 180	Lys	Asn	Lys	Val	Cys 185	Gly	His	Thr	Tyr	Glu 190		Asp	
Ala	He	Val 195	Arg	Met	Ile	Glu	Ser 200	Arg	Gln	Lys	Arg	Lys 205	Lys	Lys	Ala	
Tyr	Cys 210	Pro	Gln	He	Gly	Cys 215	Ser	His	Thr	Asp	Ile 220	Arg	Lys	Ser	Asp	
Leu 225	He	Gln	Asp	Glu	Ala 230	Leu	Arg	Arg	Ala	Ile 235	Glu	Asn	His	Asn	Lys 240	
Lys	Arg	His	Arg	His 245	Ser	Glu										
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			DNA Homo	sap	oiens	5										
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				_	ature	9										
				(9		_										
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		<00														
	gct															48
met 1	Ala	ษเน	หเร	Ala 5	ыу	rro	arg	Leu	Pro 10	Leu	vai	Leu	Lys	Thr 15	Leu	

					-		-		acc Thr		96
						_		_	ctc Leu	•	144
									gac Asp		192
									ctg Leu		240
									ctc Leu 95		288
									cca Pro		336
									gtg Val		384
									atc Ile		432
									atc Ile		480
									gac Asp 175		528
									cac His		576

_	_		_	_	gtg Val	-	•	-	_			•	_	-	624
					gca Ala 215										672
		-	_		 cga Arg	-	_				-				720
					atg Met					-	_	_		_	768
					ttc Phe			_	_	_				•	816
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					ctc Leu								tag *		957

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<213> Homo sapiens

<220>

<221> VARIANT

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ggt Gly							-	-				96
atc Ile												144
aat Asn 50												192
gtg Val												240
gga Gly	-			_		-		_	_			288
tca Ser												336
aag Lys												384
gac Asp 130												432

					acc Thr 150					_	_	_		-		480
					agg Arg											528
					ttt Phe		-		_				-	_	•	576
	_				gcc Ala	_	-			_		_	_	_	_	624
-	-		_		gaa G1u			_			_		_	_		672
	_	_		_	gaa Glu 230	_				•	•			•		720
					agt Ser									-	_	768
-				_	gca Ala			_			_		-			816
					gga Gly										-	864
					acc Thr											912
				-	cag Gln 310	-	_	_					_		_	960

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<211> 368

<212> PRT

<213> Homo sapiens

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				165					170					175		
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Leu	Ser	Asn 195	Pro	Gly	Ala	Leu	Asp 200	Leu	Pro	Ser	Leu	Thr 205	Ser	Leu	Leu	
Ser	Glu 210	Lys	Ala	Lys	Glu	Phe 215	Leu	Met	Glu	Asn	Arg 220	Val	Gln	Ser	Phe	
Tyr 225	Gln	Gln	Glu	Leu	G1u 230	Met	Val	Glu	Ser	Leu 235	Leu	Ser	Leu	Ala	Asn 240	
Gln	Pro	Val	He	His 245	Ser	Ala	Cys	Ser	Asp 250	G1n	Val	Asn	Phe	Lys 255	Lys	
Asp	Thr	Thr	Ser 260	Lys	Ala	He	His	Ser 265	He	Phe	Lys	Asn	Ala 270	He	Gln	
Leu	Leu	G1n 275	Glu	Lys	Gly	Leu	Va1 280	Phe	Gln	Lys	Asp	Asp 285	Gly	Phe	Asp	
Asn	Leu 290	Tyr	Tyr	Val	Thr	Arg 295	Glu	Asp	Lys	Asp	Leu 300	His	Arg	Lys	He	
305					G1n 310					315					320	
				325	His				330					335	-	
			340		Ala			345					350			
Asp	Gln	Ser 355	Asp	Ile	Val	Ser	Thr 360	Met	Glu	His	Tyr	Tyr 365	Thr	Ala	Phe	
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		220> 221>	CDS													
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					gtc Val											96

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							gaa Glu		192
							cgg Arg		240
							agg Arg		288
							agc Ser		336
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							cac His		480
							cag Gln		528
		gtc Val			taa *				558

<210> 296

<211> 185

<212> PRT

<213> Homo sapiens

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			20					25					30				
-			_			cta Leu	_	_	_	_							144
_		-			_	gac Asp 55		-	-		-	-		-			192
-			-		_	cat His	-	-	_		-	-	-		-	,	240
•		-	_	_		cga Arg				-	_	_		_	_		288
						cag Gln								-			336
						gtg Val											384
		-			-	cag Gln 135				_	-	-					432
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<211> 166

<212> PRT

<213> Homo sapiens

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G1n	Pro	Leu 35	Leu	Lys	Gly	Leu	Leu 40	Ser	Gly	Gln	Thr	Ser 45	Pro	Thr	Asn		
Ala	Lys 50	Leu	Glu	Lys	Leu	Asp 55	Ser	Gln	Gln	Val	Leu 60	Gln	Leu	Cys	Leu		
Arg 65	Tyr	Gln	Asp	His	Leu 70	His	Gln	Cys	Ala	G1u 75	Ala	Val	Ala	Phe	Asp 80		
G1n	Asn	Ala	Leu	Va1 85	Lys	Arg	Ile	Lys	G1u 90	Met	Asp	Leu	Ser	Va1 95	Glu		
Thr	Leu	Phe	Ser 100	Phe	Met	Gln	Glu	Arg 105	Glin	Lys	Arg	Tyr	Ala 110	Lys	Tyr		
Ala	Glu	G1n 115	He	Gln	Lys	Val	Asn 120	Glu	Met	Ser	Ala	Ile 125	Leu	Arg	Arg		
He	Gln 130	Met	Gly	He	Asp	G1n 135	Thr	Val	Pro	Leu	Leu 140	Asp	Arg	Leu	Asn		
Ser 145	Met	Leu	Pro	Glu	Gly 150	Glu	Arg	Leu	Glu	Pro 155	Phe	Ser	Met	Lys	Pro 160		
Asp	Arg	Glu	Leu	Arg 165	Leu												
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		20				25	٠				30			
				tta Leu			_						-	144
		-	_	gct Ala 55		-		_	-	-	-	-	-	192
				gga Gly	-	_		-	_	-	_			240
				aca Thr				-				-	-	288
				ctt Leu	_				_	-	-		•	336
				tca Ser					-				_	384
				gcc Ala 135										432
				aga Arg										480
				ttt Phe										528
				gat Asp										576
	•			atg Met		-			-	_			-	624

		195					200					205				
_	gga Gly 210	-		-	_	_				-				_	•	672
	cag G1n											-		-		720
	aag Lys	-								-					-	768
	gga Gly	-	_			-		-	-					_		816
	tat Tyr		tga *		٠				•							828
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	Ala	Ala	Asp 20		Leu	Asn	Arg	Arg 25		He	Val	Gln	Asp 30		Gly	
Cys	Leu	Pro 35	Gly	Leu	He	Leu	Phe 40	Met	Asp	His	Pro	Asn 45	Pro	Pro	Val	
Val	His 50	Ser	Ala	Leu	Leu	A1 a 55	Leu	Arg	Tyr	Leu	Ala 60	Glu	Cys	Arg	Ala	
Asn 65	Arg	Glu	Lys	Met	Lys 70	Gly	Glu	Leu	Gly	Met 75	Met	Leu	Ser	Leu	G1n 80	

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Asn	Va1	He	Gln	Lys 85	Thr	Thr	Thr	Pro	G1y 90	Glu	Thr	Lys	Leu	Leu 95	Ala	
Ser	Glu	He	Tyr 100	Asp	He	Leu	Gln	Ser 105	Ser	Asn	Met	Ala	Asp 110	Gly	Asp	
Ser	Phe	Asn 115	Glu	Met	Asn	Ser	Arg 120	Arg	Arg	Lys	Ala	Xaa 125		Phe	Leu	
Gly	Thr 130	Thr	Asn	Lys	Arg	Ala 135	Lys	Thr	Val	Val	Leu 140		Пe	Asp	Gly	
Leu 145	Asp	Asp	Thr	Ser	Arg 150	Arg	Asn	Leu	Cys	Glu 155	Glu	Ala	Leu	Leu	Lys 160	
	Lys	Gly	Val	Ile 165		Phe	Thr	Phe	G1n 170		Ala	Val	Gln	Arg 175		
Val	Val	Arg	Ile 180	Arg	Ser	Asp	Leu	Lys 185	Ala	Glu	Ala	Leu	Ala 190	Ser	Ala	
He	Ala	Ser 195	Thr	Lys	Val	Met	Lys 200	Ala	Gln	Gln	Val	Val 205	Lys	Ser	Glu	
Ser	Gly 210	Glu	Glu	Met	Leu	Val 215	Pro	Phe	Gln	Asp	Thr 220	Pro	Val	Glu	Val	
G1u 225	Gln	Asn	Thr	Glu	Leu 230	Pro	Asp	Tyr	Leu	Pro 235	Glu	Asp	Glu	Ser	Pro 240	
	Lys	Glu	Gln	Asp 245		Ala	Val	Ser	Arg 250		Gly	Ser	His	Pro 255		
Gly	Gly	Ala	Ser 260		Leu	Ser	Thr	Ala 265		Asn	Phe	Leu	Ser 270	Arg	Ser	
Phe	Tyr	Trp 275	200					203					270			
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		212>														
				sap	oiens	5										
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				_	ature											-
					1101)											
	<'	223>	n =	Α, Ι	.C or	^ G										
		100>						, .						_		
														cgt Arg		48
1	ΛIα	JCI	лια	5	Leu	JCI	JC1	vai	10	1111	1111	AId .	שכו	15	FIIC	

						gaa Glu 30		
						gga Gly		. 144
						aag Lys		192
						ttt Phe		240
						cat His		288
						aat Asn 110		336
						ttt Phe		384
						gaa Glu		432
						tcc Ser		480
						gac Asp		528
						att Ile 190		576

			tct Ser									624
			gat Asp 215	_	-					_	-	672
			aca Thr	-				_		_		720
			gaa Glu									768
			gaa G1u									816
			tgg Trp									864
		_	aaa Lys 295	_		_	_	 _	_		-	912
			caa G1n									960
			act Thr									1008
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			aac Asn							tga *		· 1101



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				245					250					255		
Arg	Leu	Lys	Leu 260	Glu	Leu	Glu	Arg	Lys 265	Asp	Ala	Glu	He	G1n 270	Lys	Leu	
Lys	Asn	Val 275	Пe	Thr	Gln	Trp	G1u 280	Ala	Lys	Tyr	Lys	G1u 285	Val	Lys	Ala	
Arg	Asn 290	Ala	Gln	Leu	Leu	Lys 295	Met	Leu	Gln	Glu	Gly 300	Glu	Met	Lys	Asp	
Lys 305	Ala	Glu	Пe	Leu	Leu 310	Gln	Val	Asp	Glu	Ser 315		Ser	He	Lys	Asn 320	
Glu	Leu	Thr	Пe	G1n 325		Thr	Ser	Leu	His 330		Ala	Leu	Glu	G1n 335		
Arg	Ser	Lys	Val 340		Val	Leu	Gln	A1a 345		Leu	Ala	Lys	Tyr 350		Gly	
Gly	Arg	Lys 355		Lys	Arg	Asn	Ser 360		Ser	Asp	Gln	Cys 365				
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	acc Thr			Leu	Tyr	Leu		Leu	Ala		_		_	-	_	96
aac																
	ttg Leu															144
Asn cct		Glu 35 aat	Lys cct	Thr tgg	Ile aac	Phe tgg	Cys 40 ggc	Leu aaa	Gln ttg	Lys gca	Leu gag	Ile 45 gct	Ser tac	Leu	His aat	144 192

65					70					75					80	
				•	-									cac His 95		288
		-	_		-	-			-		-			agc Ser		336
														gag G1u		384
_	_						-	-	-	-	-	_	_	aca Thr		432
				_	_		-	-	-				_	acc Thr	agg _. Arg 160	480
			-					-			-		-	ttg Leu 175		528
					_	-	-		-	-		_		999 Gly		576
_			_	-		_	_	_		_		•	_	gga Gly	_	624
														aag Lys		672
														gaa Glu		720
										•			_	cca Pro		768

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448

245 250 255

gaa aat cag ttc cat aca gag ata caa atc ttg gct tag Glu Asn Gln Phe His Thr Glu Ile Gln Ile Leu Ala * 260 265 807

<210> 304

<211> 268

<212> PRT

<213> Homo sapiens

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Phe Glu Asp Lys Trp Phe Arg Lys Ile Lys Asp His Phe Cys Pro Phe

235

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Glu	Asn	Gln	Phe 260	245 His	Thr	Glu	Ile	G1n 265	250 Ile	Leu	Ala			255		
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	<2	220> 221> 222>		(8	310)											
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	ctg Leu															96
	cgc Arg						_		_	_		_	_		_	144
_	gct Ala 50		-			_			-	-						192
	ttg Leu															240
	atc Ile			_		_			_				-		•	288
	ctt Leu															336
	ctt Leu															384

		115					120					125				
	_		-	-	-					gtc Val		-	_		• •	432
			_				-		-	gtg Val 155			_			480
_				~ ~	•	•	•		_	cag Gln	-			•		528
	_	_			_			-	_	ttc Phe					-	576
-	-					-		-		att Ile	_				-	624
-	-	_		_	_				_	gat Asp	_	-	-			672
			_		_					aaa Lys 235			_			720
		-				_	-		-	ttt Phe		_	_	-		768
-	-	_	-	-			_			gag Glu			taa *			810

<210> 306

<211> 269

<212> PRT

<213> Homo sapiens

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Thr	Leu	Cys	Phe 20	Ala	Val	Thr	Gly	Arg 25	Ser	Tyr	Ser	He	Phe 30	Asp	Asn
Asn	Arg	Gln 35	Asp	Pro	Thr	Gly	Leu 40	Thr	Ala	Ala	Leu	G1n 45	Ala	Thr	Asp
Leu	A1 a 50	Gly	Val	Leu	His	Met 55	Leu	Tyr	Cys	Val	Leu 60	Phe	His	Gly	Thr
Ile 65	Leu	Asp	Pro	Ser	Thr 70		Ser	Pro	Lys	G1u 75	Asn	Tyr	Thr	Gln	Asn 80
				85					90					Phe 95	•
Ala	Leu	His	Leu 100	Pro	Ala	Phe	Gln	Ser 105	He	Val	Gly	Ala	Glu 110	Gly	Leu
Ser	Leu	Ala 115	Phe	Arg	His	Met	Ala 120	Ser	Ser	Leu	Leu	Gly 125	His	Cys	Ser
Gln	Val 130	Ser	Cys	Glu	Ser	Leu 135	Leu	His	Glu	Val	Ile 140	Val	Cys	Val	Gly
145					150					155				Ser	160
Arg	His	Pro	Thr	Val 165	Leu	Gln	Lys	Leu	Cys 170	Gln	Leu	Pro	Phe	G1n 175	Tyr
		·	180					185					190	Пe	
		195					200					205		Glu	
	210					215					220			Thr	
225					230					235	_	_		Leu	240
		•	•	245					250				Gln	A1a 255	Trp
Glu	Glu	Ala	Arg 260	Gln	Phe	Phe	Leu	Lys 265	Lys	Glu	Lys	Lys			
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cag	aac	aag						ctg Leu 10							48
								tct Ser		_	-			_	96
	-	_	-	_				cgc Arg	•	-			_	_	144
								ttc Phe							192
				-	_	_	-	atc Ile		_		_		- , -	240
				_	-		_	gat Asp 90			_	_			288
								ttg Leu							336
						-	_	cag G1n		-	_				384
								ctg Leu				_			432
								ctg Leu							480
								gtg Val					-		528

				165					170					175		
	cca Pro															576
	ttt Phe				_			-	_					_		624
_	ata Ile 210		-										•			672
-	atg Met	-	_	_		_	_						_	•	_	720
-	tac Tyr	-			_	-	-		_		_			•	att Ile	768
	aat Asn							_			_	_		_	_	816
-	cta Leu	-		tag *												831
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Met 1	Gln	Asn	Lys	Val 5	Thr	Gln	Leu	Val	Leu 10	Ser	Ala	Leu	Gln	Ser 15	Leu	
Thr	Asp	Thr	Leu 20	Leu	Phe	Pro	Phe	Tyr 25	Ser	Gly	Pro	Ser	Gly 30		Leu	
Lys	Thr	A1 a 35		Leu	Asp	Tyr	Ile 40		Arg	Cys	Arg	Pro 45		Asp	Ser	
Glu	Lys		Asn	Met	He	Ala		Cys	Phe	Ser	Met	_	Arg	Glu	Ile	

	50					55					60					
Gly 65	Glu	Asn	His	Glu	Ala 70	Ala	Ala	Arg	He	G1n 75	Leu	Lys	Leu	He	Glu 80	
Ser	Gln	Pro	Trp	G1u 85	Asp	Ser	Leu	Lys	Asp 90	Gly	His	Gln	Leu	Lys 95	Gln	
Leu	Leu	Leu	Lys 100	Ala	Leu	Thr	Leu	Met 105	Leu	Asp	Ala	Ala	Glu 110	Ser	Tyr	
Ala	Lys	Asp 115	Ser	Cys	Val	Arg	G1n 120	Ala	Gln	His	Cys	G1n 125	Arg	Leu	Thr	
	Leu 130					135					140	,				
145	Leu				150					155	·	•			160	
	Pro			165					170					175		
	Pro		180					185					190		·	
	Phe	195	-				200	•			·	205		Ū		
	11e 210					215					220					٠
225	Met -				230				•	235		•	•		240	
	Tyr			245					250					255		
	Asn		260	Leu	Lys	Asp	Pro	GIn 265	Ihr	Gly	Cys	Cys	Leu 270	Lys	Asp	
met	Leu	275	Gly													
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Met	agg Arg			Asp				_	His	-				Thr	gtt Val	48
1				5					10					15		

		gct Ala														96
		tat Tyr 35											-	_	-	144
		aac Asn				_			-	-					-	192
		aga Arg	-	_		-	_			_						240
-		gag Glu	_		-	_			-	-		-	_		-	288
		gtg Val														336
_		cac His 115		_			-		-	taa *						369
	<2 <2	210> 211> 212> 213>	122 PRT	sa;	oiens	S										
		400>														
Met 1	Arg	Thr	He	Asp 5	Asp	Arg	He	Val	His 10	Glu	Leu	Asn	Thr	Thr 15	Val	
Pro	Thr	Ala	Ser 20	Phe	Ala	Gly	Lys	11e 25	Asp	Ala	Ser	Gln	Thr 30	Cys	Lys	
Gln	Leu	Tyr 35	Glu	Ser	Leu	Met	A1a 40		His	Ala	Ser	Arg 45		Arg	Val	
He	Lys 50	Asn	Cys	Пe	Ala	G1n 55		Ser	Ala	Val	Va1 60		Asn	Leu	Arg	
Glu		Arg	Glu	Lys	Asn		Asp	Asp	Leu	Thr		Leu	Lys	Gln	Leu	

65					70					75					80		
Arg	Lys	Glu	Gln		Lys	Leu	Lys	Trp		Gln	Ser	Glu	Leu		Val		
Glu	Glu	Val	Val	85 Asn	Δsn	Arg	Ser	Trn	90 Lvc	Val	Dha	Acn	Glu	95 Ara	Cvc		
a.u	uiu	vui	100	ASII	vah	Al 9	JC1	105	Lys	Vai	riie	ASH	110	Ary	Cys		
Arg	He	His 115	Phe	Lys	Pro	Pro	Lys 120	Asn	Glu								
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1				5					10					15			
ggt	ссс	cgg	gcg	gcg	ggg	gcc	caa	ggc	ctg	acc	cag	act	ccg	acc	gaa		96
			Ala			Ala		Gly									
			20					25					30				
atg	cag	cgg	gtc	agt	tta	cgc	ttt	ggg	qqc	CCC	atq	acc	cqc	agc	tac	1	44
						Arg											
		35					40					45					
caa	agc	acc	acc	caa	act.	ggt	ct.t.	ccc	caa	ลลด	aca	agg	ata	atc	cta	1	92
						Gly										1	,,
	50					55				_	60						
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						Met										2	40
65	•			[70			Р		75	,		, u	u.,	80		
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Αια	Aia	Ala	uiu	85	Leu	Ala	Ald	IUI.	90	2er	Inr	ыу	Pne	ser 95	Arg		
				50					70),			
tcg	tcc	gcc	att	aac	gag	gag	gat	999	tct	tca	gaa	gag	999	gtt	gtg	33	36
Ser	Ser	Ala	He	Asn	Glu	Glu	Asp	Gly	Ser	Ser	Glu	Glu	Gly	Val	Val		

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Met	Gln	Arg 35		Ser	Leu	Arg	Phe 40		Gly	Pro	Met	Thr 45		Ser	Tyr	
Arg	Ser 50		Ala	Arg	Thr	G1y 55		Pro	Arg	Lys	Thr 60		He	Пe	Leu	
G1u 65	Asp	Glu	Asn	Asp	Ala 70		Ala	Asp	Ala	Asp 75		Leu	Ala	Gly	Pro 80	•
	Ala	Ala	Glu	Leu 85		Ala	Ala	Thr	Va1 90	. •	Thr	Gly	Phe	Ser 95		
Ser	Ser	Ala	Ile 100		Glu	Glu	Asp	Gly 105		Ser	Glu	Glu	Gly 110		Val	
He	Asn	Ala		Ala	Leu	Glv	Pro		Ala	Leu	Pro	i eu		Val	Glv	

		115					120					125				
His	His 130	Glu	Pro	Glu	Pro	Va1 135	Trp	Glu	Ala	Ala	Arg 140	Pro	Phe	Arg	Ala	
Pro 145	Ser	Ser	Trp	Gly	Ala 150	Glu	Pro	Ala	Pro	His 155	Gly	Ala	Gln	Ala	Leu 160	
His	Leu	Ser	Thr	Met 165	Ser	Leu	Gln	Pro	Thr 170	Ser	Gly	Arg	Val	Pro 175		
Gly	His	Lys	Ser 180	Leu	Tyr											
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	cca Pro 50															192
	cag Gln							•	_	tga *						225

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Leu Phe Asn Ser Val Ala Phe Gln Asn Ala Asp Ala Thr Arg Arg Thr
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Cys Pro Gln Leu Thr Thr Tyr Gly Cys His Gly Ser Gly Gln Leu Ser
Lys Gîn Val Pro Val Val Ser Ser Ala Val
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ccg ctg tgg tcc tcc tca ctg cct ggg ctg gac act gct gaa agt aaa
                                                                       96
Pro Leu Trp Ser Ser Ser Leu Pro Gly Leu Asp Thr Ala Glu Ser Lys
             20
                                 25
                                                      30
gcc acc att gca gac ctg atc ctg tct gcg ctg gag aga gcc acc gtc
                                                                      144
Ala Thr Ile Ala Asp Leu Ile Leu Ser Ala Leu Glu Arg Ala Thr Val
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                             40
                                                 45
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					gat Asp 60				192
					cgg Arg				240
					gtg Val				288
					cac His				336
					acc Thr				384
					gat Asp 140				432
					gag Glu				480
					gac Asp				528
					acc Thr				576
					ttc Phe		_	_	624
					agc Ser 220				672

			gcc Ala							-	-	_		-	720
			tac Tyr 245				_			_	_			_	768
			ggc Gly							_				-	816
			agc Ser												864
	-	-	gat Asp	-	-				•				_		912
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Pro	Leu	Trp	Ser 20	Ser	Ser	Leu	Pro	G1y 25	Leu	Asp	Thr	Ala	Glu 30	Ser	Lys
Ala	Thr	11e 35		Asp	Leu	He	Leu 40		Ala	Leu	Glu	Arg 45	Ala	Thr	Va1
Phe	Leu 50		Gln	Arg	Leu	Pro 55	Glu	He	Asn	Leu	Asp 60		Met	Val	Gly
Va1 65	Arg	Val	Leu	Glu	Glu 70	Gln	Leu	Lys	Ser	Va1 75	Arg	Glu	Lys	Trp	A1 a 80
Gln	Glu	Pro	Leu	Leu 85	Gln	Pro	Leu	Ser	Leu 90	Arg	Val	Gly	Met	Leu 95	Gly
Glu	Lys	Leu	Glu 100	Ala	Ala	He	Gln	Arg 105	Ser	Leu	His	Tyr	Leu 110	Lys	Leu
Ser	Asp	Pro 115	Lys	Tyr	Leu	Arg	Glu 120	Phe	Gln	Leu	Thr	Leu 125	Gln	Pro	Gly
	130					135					140		Ser		
145					150					155			Arg		160
				165					170		·		Ser	175	
	_		180	·				185				•	Pro 190	-	
	_	195					200					205	Trp		·
	210	•				215					220		Asp		
225					230					235			Ala		240
				245					250				Asn	255	
			260					265					Arg 270		
Glu	Ala	11e 275	Leu	Ser	Trp	Gln	Lys 280	Gln	Gln	Glu	Gly	Cys 285	Phe	Gly	Glu
Pro	Asp 290	Ala	Glu	Asp	Glu	G1u 295	Ser	Ser	Lys	Ala	11e 300	Gln	Tyr	Gln	Gln
His 305	Phe	Ser	Arg	Arg	Va1 310	Lys	Arg	Arg	Glu	Lys 315	Gln	Phe	Pro	Asp	G1y 320
Cys	Ser	Ser	His	Asn 325	Thr	Ala	Thr	Ala	Val 330	Ala	Ala	Leu	Gly	G1y 335	Phe
Leu	Tyr	Ile	Leu 340	Ala	Glu	Tyr	Pro	Pro 345	Ala	Asn	Arg	Glu	Pro 350	His	Pro

WO 01/29221

Ser	Thr	Pro 355	Pro	Pro	Pro	Ser	Ser 360	Arg								
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_				-					_				cga Arg	-	-	240
-		-	_			_			_			-	gcc Ala	_	-	288
_	-			_			_			-	_		gct Ala 110			336

			tac Tyr								384
			act Thr								432
			aag Lys		_			_		-	480
_	_		ggt Gly 165							Leu	528
			gcc Ala								576
			gag Glu					-			624
			aag Lys								672
			gtg Val								720
			cca Pro 245								768
			gag Glu								816
			ccc Pro								864

				cag G1n 295									912
				ttc Phe									960
				ctg Leu						_	_	_	1008
-	_	-	_	gcc Ala			 -	-	-			_	1056
				gaa Glu									1104
				agc Ser 375	-	-	_	_	_				1152
				ctg Leu									1200
 _		_		cta Leu			-				•	_	1248
				ggg Gly									1296
				ggt Gly									1344
				atc Ile 455									1392

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Pro Leu Leu Lys Lys Gln Gly Trp Asp Trp Ala Leu Pro Val Ala Lys



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Phe	Leu	Thr	Phe	Pro 245	Gly	Leu	Arg	Leu	Ala 250	Gln	Thr	His	Arg	Asp 255	Ala
Leu	Thr	Met	Ser 260	Glu	Asp	Arg	Pro	Met 265		Gln	Phe	Leu	Leu 270		Thr
Ser	Phe	Leu 275		Pro	Leu	Phe	I le 280		Trp	Leu	Trp	Thr 285	Lys	Pro	He
Λla	۸ra		Dho	Lou	Uic	C12		Dno	Dha	C1.,	C1		A	Dla a	C
	290					295					300		Arg		
Leu 305	Leu	Ser	Asp	Ser	Ala 310	Phe	Asp	Ser	Gly	Arg 315	Leu	Trp	Leu	Leu	Va1 320
Val	Leu	Cys	Leu	Leu 325	Arg	Leu	Ala	Val	Thr 330	Arg	Pro	His	Leu	G1n 335	
Tyr	Leu	Cys	Leu 340	Ala	Lys	Ala	Arg	Val 345		Gln	Leu	Arg	Arg 350		Ala
Gly	Arg	I le 355		Ala	Arg	Glu	Ile 360		Gln	Arg	Val	Va1 365	Arg	Val	Tyr
Cys	Tyr 370		Thr	Val	Val	Ser 375		Gln	Tyr	Leu	Thr 380		Leu	Пе	Leu
Thr		Δsn	Cvs	Thr	Lau		Lau	Lvc	Thr	Lou		Clv	Tyr	con	Tnn
385					390			•		395					400
Gly	Leu	Gly	Pro	A1a 405	Pro	Leu	Leu	Ser	Pro 410	Asp	Pro	Ser	Ser	Ala 415	Ser
Ala	Ala	Pro	Ile 420	Gly	Ser	Gly	Glu	Asp 425	Glu	Val	Xaa	Gln	Thr 430	Ala	Ala
Arg	Пe	A1a 435	Gly	Ala	Leu	Gly	Gly 440	Leu	Leu	Thr	Pro	Leu 445	Phe	Leu	Arg
Gly	Va1 450	Leu	Ala	Tyr	Leu	I le 455	Trp	Trp	Thr	Ala	A1a 460	Cys	Gln	Leu	Leu
Ala	Ser	Leu	Phe	Gly	Leu		Phe	His	Gln	His		Ala	Gly	Ser	
465					470	•				475					
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														cca Pro		96
														gaa Glu		144
														gtg Val		192
														atg Met		240
aaa Lys	cta Leu	gct Ala	ggt Gly	ttg Leu 85	Val	gaa Glu	gag G1u	ctg Leu	gag Glu 90	gct Ala	gac Asp	gag Glu	tgg Trp	cgg Arg 95	ttt Phe	288
						ctg Leu								tga *		333
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Ser	Val	Thr	G1y 20	Ser	Gly	Phe	Ser	Va1 25		Asp	Leu	Ala	Pro 30	Pro	Arg	
Lys	Ala	Leu		Thr	Tyr	Pro	Lys		Ala	Gly	Glu	Met		Glu	Asp	

35 40 45 Gly Ser Glu Arg Phe Leu Cys Glu Ser Val Phe Ser Tyr Gln Val Ala

Ser Thr Leu Lys Gln Val Lys His Asp Gln Gln Val Ala Arg Met Glu

65					70					75					80	
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Lys	Pro	He	Glu 100	Gln	Leu	Leu	Gly	Phe 105	Thr	Pro	Ser	Ser	Gly 110			
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gaa Glu	999 Gly	gat Asp	gta Val 20	atg Met	cag G1n	ctg Leu	aaa Lys	tca Ser 25	gaa Glu	gcc Ala	atc Ile	cag Gln	acc Thr 30	tct Ser	cat His	96
ttt Phe	caa G1n	ggc Gly 35	aga Arg	ctt Leu	aat Asn	gaa G1u	gtc Val 40	att Ile	aga Arg	acc Thr	tta Leu	act Thr 45	cag G1n	gtc Val	att Ile	144
agt Ser	gtc Val 50	tct Ser	999 Gly	gtg Val	att Ile	ggt Gly 55	ctc Leu	cag Gln	tca Ser	aat Asn	gca Ala 60	gtc Val	tgg Trp	ctt Leu	ctt Leu	192
gga Gly 65	cat His	ctt Leu	cat His	cta Leu	tct Ser 70	act Thr	cta Leu	tcc Ser	tca Ser	agt Ser 75	caa Gln	agt Ser	aga Arg	gcc Ala	tct Ser 80	240
gtt /al	cct Pro	act Thr	gac Asp	tat Tyr 85	agc Ser	tac Tyr	ttg Leu	cct Pro	gaa Glu 90	agc Ser	agt Ser	ttt Phe	att Ile	gga Gly 95	gca Ala	288

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					gta Val					_		_		384
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	_				ggt Gly	-		_		_	_		_	480
	_		•	-	cag Gln		_		•	-	_		_	528
	_				cca Pro	_		-	-	_	_			576
_	_		-		tct Ser	-	_							624
					ttt Phe 215	-			_		-	_		672
					gga Gly									720
					atg Met									768
		_		-	gct Ala					-		_		816

	-		 -	_	-		-	_		atc Ile	_		_		864
			-		_					cgg Arg 300		_	_	•	912
	-	_		-		_	-		_	aaa Lys	_			_	960
					_			_		gat Asp	_	_	_		1008
-		_	 -	-		_	-			gcc Ala					1056
									-	gag Glu			-	•	1104
										atg Met 380					1152
									-	atg Met	-	_	•	_	1200
_				-	-	_		•	•	ttc Phe		•			1248
										tca Ser					1296
										gtt Val					1344

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                                                45
Ser Val Ser Gly Val Ile Gly Leu Gln Ser Asn Ala Val Trp Leu Leu
Gly His Leu His Leu Ser Thr Leu Ser Ser Ser Gln Ser Arg Ala Ser
Val Pro Thr Asp Tyr Ser Tyr Leu Pro Glu Ser Ser Phe Ile Gly Ala
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Ala Ile Gly Phe Phe Ile Thr Gly Gly Lys Lys Gly Pro Glu Ser Val
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                                105
Pro Pro Ser Leu Leu Lys Val Val Met Lys Pro Ile Ala Thr Val Gly
                            120
Glu Ser Tyr Gln Tyr Pro Pro Val Asn Trp Ala Ala Leu Leu Ser Pro
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                                            140
Leu Met Arg Leu Asn Phe Gly Glu Glu Ile Gln Gln Leu Cys Leu Glu
145
                    150
                                        155
                                                             160
Ile Met Val Thr Gln Ala Gln Ser Ser Gln Asn Ala Ala Ala Leu Leu
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                                    170
Gly Leu Trp Val Thr Pro Pro Leu Ile His Ser Leu Ser Leu Asn Thr
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                                185
Lys Arg Tyr Leu Leu Ile Ser Ala Pro Leu Trp Ile Lys His Ile Ser
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Asp Glu Gln Ile Leu Gly Phe Val Glu Asn Leu Met Val Ala Val Phe
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                        215
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Trp	Ser	Leu	Leu 260	Ser	Glu	Ala	Thr	Gly 265	Lys	He	Phe	Asp	Leu 270	Leu	Pro
Asn	Lys	I1e 275	Arg	Arg	Lys	Asp	Leu 280	Glu	Leu	Tyr	Ile	Ser 285	He	Ala	Lys
Cys	Leu 290	Leu	Glu	Met	Thr	Asp 295	Asp	Asp	Ala	Asn	Arg 300	He	Ala	Gln	Val
Thr 305	Lys	Ser	Asn	He	G1u 310	Lys	Ala	Ala	Phe	Val 315	Lys	Leu	Tyr	Leu	Va1 320
				325					330		•	Met		335	
			340					345				Pro	350		
		355					360					Asn 365	_		
	370					375		_			380	His			
385					390					395		Ala			400
				405					410			Ile		415	
			420					425				Ala	430		
		435					440					Leu 445	Pro	Glu	Phe
Lys	Lys 450	Lys	Ąlа	Val	Trp	Thr 455	Arg	Ala	Tyr	Gly	Trp 460				
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			tct Ser 70			_	_	-	_	240
			agc Ser							288
			att Ile							336
			aaa Lys							384
			cct Pro							432
			ttt Phe 150							480
			gca Ala							528

	_				cca Pro		-			-	_	-	-			576
-	-			_	ata Ile		-		•							624
_	-	_		-	ggt Gly		•	-			_	-	-	•		672
	-				ctt Leu 230		_				-		-	•		720
		_	_	-	gcc Ala	•		•		-		•				768
	_	_			gaa Glu	-						-		-		816
	_			-	aag Lys	-			-			-		_		864
_			-	-	aca Thr		-	_	-				-	_	-	912
					gaa Glu 310			_		-		_			-	960
					ccc Pro											1008
					gag Glu											1056

			cgg Arg										1104
			ctc Leu								_		1152
			tcc Ser 390		_	_		_		_	_	:	1200
		_	ata Ile	-	_		-	-		-	•	-	1248
			ctc Leu		-	_	_		_		~ ~		1296
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			gtc Val	-	-	-							1392
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			tcc Ser		-		-		_	-			1536
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Ser Val Ser Gly Val Ile Gly Leu Gln Ser Asn Ala Val Trp Leu Leu
                        55
Gly His Leu His Leu Ser Thr Leu Ser Ser Ser Gln Ser Arg Ala Ser
                                        75
Val Pro Thr Asp Tyr Ser Tyr Leu Pro Glu Ser Ser Phe Ile Gly Ala
Ala Ile Gly Phe Phe Ile Thr Gly Gly Lys Lys Gly Pro Glu Ser Val
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                                105
Pro Pro Ser Leu Leu Lys Val Val Met Lys Pro Ile Ala Thr Val Gly
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                                                125
Glu Ser Tyr Gln Tyr Pro Pro Val Asn Trp Ala Ala Leu Leu Ser Pro
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Leu Met Arg Leu Asn Phe Gly Glu Glu Ile Gln Gln Leu Cys Leu Glu
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Ile Met Val Thr Gln Ala Gln Ser Ser Gln Asn Ala Ala Leu Leu
                165
                                    170
Gly Leu Trp Val Thr Pro Pro Leu Ile His Ser Leu Ser Leu Asn Thr
           180
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Lys Arg Tyr Leu Leu Ile Ser Ala Pro Leu Trp Ile Lys His Ile Ser
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Asp Glu Gln Ile Leu Gly Phe Val Glu Asn Leu Met Val Ala Val Phe
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Lys	Ala	Ala	Ser	Pro	Leu	Gly	Ser	Pro	Glu	Leu	Cys	Pro	Ser	Ala	Leu
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His	Gly	Leu	Ser	Gln	Ala	Met	Lys	Leu	Pro	Ser	Pro	Ala	His	His	
				245			•		250					255	
Trp	Ser	Leu	Leu 260	Ser	Glu	Ala	Thr	Gly 265	Lys	He	Phe	Asp	Leu 270		Pro
Asn	Lys	11e 275	Arg	Arg	Lys	Asp	Leu 280	Glu	Leu	Tyr	Ile	Ser 285	Пe	Ala	Lys
Cys	Leu 290	Leu	Glu	Met	Thr	Asp 295		Asp	Ala	Asn	Arg 300	He	Ala	GIn	Val
Thr 305	Lys	Ser	Asn	He	Glu 310	Lys	Ala	Ala	Phe	Val 315	Lys	Leu	Tyr	Leu	Va1 320
				325					330				Leu	335	
			340					345					11e 350		
Ser	Leu	Tyr 355	Gln	Ala	Arg	He	Val 360	Ser	His	Ala	Asn	Thr 365	Gly	Val	Leu
	370					375				_	380		Arg		
A1a 385	Tyr	Gln	Ser	Thr	Ser 390	Phe	His	Asn	Thr	A1a 395	Leu		Glu	Ala	Leu 400
Asp	Phe	Phe	Leu	Leu 405	He	Phe	Ala	Thr	Ala 410	Val	۷a٦	Ala	Trp	Ala 415	Asp
His	Thr	Ala	Pro 420	Leu	Leu	Leu	Gly	Leu 425	Ser	Ala	Ser	Trp	Leu 430	Pro	Trp
His	Gln	G1u 435			Pro				Val			Phe 445	Leu	Gly	Arg
Ser	Pro 450	Met	His	Arg	Val	Thr 455	Leu	Gln	Glu	Val	Leu 460	Thr	Leu	Leu	Pro
Asn 465	Ser	Met	Ala		Leu 470		Gln	Lys	Glu	Pro 475	-	Lys	Glu	Gln	Thr 480
Gln	Lys	Phe	He	Asp 485	Trp	Leu	Phe	Ser	I1e 490	Met	Glu	Ser	Pro	Lys 495	Glu
Ala	Leu	Ser	A1a 500	Gln	Ser	Arg	Asp	Leu 505	Leu	Lys	Ala	Thr	Leu 510	Leu	Ser
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<211> 666

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 tca Ser	-	-	-		-		_	-	_		•	-	-	•	288
ggc Gly												_	_	-	336
gcc Ala					_				_	-		-		_	384
 gcc Ala 130			_		_			_			_	•	•		432

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	ggc Gly										-		-			528
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Trp	Val	Arg	Gly 20	Ser	Gly	Pro	Ser	Va1 25	Leu	Ser	Arg	Leu	G1n 30	Asp	Ala	
Ala	Val	Va1 35	Arg	Pro	Gly	Phe	Leu 40	Ser	Thr	Ala	Glu	Glu 45	Glu	Thr	Leu	
Ser	Arg 50	Glu	Leu	Glu	Pro	G1u 55	Leu	Arg	Arg	Arg	Arg 60	Tyr	Glu	Tyr	Asp	
His 65	Trp	Asp	Ala	Ala	I1e 70	His	Gly	Phe	Arg	Glu 75	Thr	Glu	Lys	Ser	Arg .	
	Ser	G1u	Ala	Ser 85		Ala	He	Leu	G1n 90		Val	Gln	Ala	A1a 95		
Phe	Gly	Pro	Gly 100		Thr	Leu	Leu	Ser 105		Val	His	Val	Leu 110		Leu	
Glu		Ana		Tun	110	1 40	Dno		Val	A	Can	110		Dho	Cuc	
	Ala	115	ыу	ıyı.	He	Lys	120	1112	Vai	ASP	Set.	125	Lys	rne	cys	

	130					135					140					
Leu 145	Val	His	Thr	Gln	G1u 150	Pro	Gly	Glu	Trp	Leu 155	Glu	Leu	Leu	Leu	Glu 160	
Pro	Gly	Ser	Leu	Tyr 165	He	Leu	Arg	Gly	Ser 170	Ala	Arg	Tyr	Asp	Phe 175	Ser	
His	Glu	He	Leu 180	Arg	Asp	Glu	Glu	Ser 185	Phe	Phe	Gly	Glu	Arg 190	Arg	Ile	
Pro	Arg	Gly 195	Arg	Arg	Ile	Ser	Va1 200	He	Cys	Arg	Ser	Leu 205	Pro	Glu	Gly	
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-	gac Asp					-			-					_	-	96
	tta Leu				Ser	Thr		Tyr	-		_		-		_	144
	gaa Glu 50		_			_	-		_	-				-	-	192
	ata Ile		_		_	_						_	_	-		240
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482

85 90 95

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<211> 97

<212> PRT

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Asn Leu Leu Ile Gly Ser Thr Ser Tyr Val Glu Glu Met Pro Gln
35 40 45

Ile Glu Thr Arg Val Ile Leu Val Gln Glu Ala Gly Lys Gln Glu Glu 50 55 60

Leu Ile Lys Ala Leu Lys Asp Ile Lys Val Gly Phe Val Lys Met Glu 65 70 75 80

Ser Val Glu Glu Phe Glu Gly Leu Asp Ser Pro Glu Phe Glu Met Tyr 85 90 95

Leu

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1 5 10 15

ttc tgc ctc ctg tgg ccc ctc gtg gtg aag ggc tgc acg atg atc cgg 96 Phe Cys Leu Leu Trp Pro Leu Val Val Lys Gly Cys Thr Met Ile Arg

20 25 30 tgg aag ata aac aac ctc att gcc tca gaa tcc tac tac acc tac gcc 144 Trp Lys Ile Asn Asn Leu Ile Ala Ser Glu Ser Tyr Tyr Thr Tyr Ala 35 40 tcc att tcc gga atc tcg agc atg cca tct ctg aga cat tcc agg atg 192 Ser Ile Ser Gly Ile Ser Ser Met Pro Ser Leu Arg His Ser Arg Met 50 ggc tcc atg ttc agc tcc agg atg aca gag gac agg gct gaa ccc aag 240 Gly Ser Met Phe Ser Ser Arg Met Thr Glu Asp Arg Ala Glu Pro Lys 65 70 80 gaa gcc gtg gag aga cag ttg atg acc tga 270 Glu Ala Val Glu Arg Gln Leu Met Thr * 85 <210> 330 <211> 89 <212> PRT <213> Homo sapiens <400> 330 Met Val Ser Ala Ser Val Phe Val Gly Leu Val Ile Phe Tyr Ile Ala 5 1 10 Phe Cys Leu Leu Trp Pro Leu Val Val Lys Gly Cys Thr Met Ile Arg Trp Lys Ile Asn Asn Leu Ile Ala Ser Glu Ser Tyr Tyr Thr Tyr Ala 40 Ser Ile Ser Gly Ile Ser Ser Met Pro Ser Leu Arg His Ser Arg Met Gly Ser Met Phe Ser Ser Arg Met Thr Glu Asp Arg Ala Glu Pro Lys 70 75 Glu Ala Val Glu Arg Gln Leu Met Thr 85 <210> 331 <211> 255

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gaa gat gat gca cgg agt gag tct agt act gaa tgg gac tta gat gga 144 Glu Asp Asp Ala Arg Ser Glu Ser Ser Thr Glu Trp Asp Leu Asp Gly 35 40 45

ttc agt gag ctg gac tct gag tca gga agt tca agt tct ttt tca gat
Phe Ser Glu Leu Asp Ser Glu Ser Gly Ser Ser Ser Phe Ser Asp
50 55 60

gat gaa gtc tgg gtg caa gta gca cct cag cga aat gca cag gat cag
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<211> 84

<212> PRT

<213> Homo sapiens

<400> 332

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25 30

Glu Asp Asp Ala Arg Ser Glu Ser Ser Thr Glu Trp Asp Leu Asp Gly 35 40 45

Phe Ser Glu Leu Asp Ser Glu Ser Gly Ser Ser Ser Phe Ser Asp 50 55 60

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atg ttt agc agg agc aag tat gca tct gct gaa aag tgg tgt ggc ctg Met Phe Ser Arg Ser Lys Tyr Ala Ser Ala Glu Lys Trp Cys Gly Leu 20 25 30 30 30 144 Gcc ttg cgt ttc ctt aac cac ctt acc tcc ttc aag gaa agc tat gaa Ala Leu Arg Phe Leu Asn His Leu Thr Ser Phe Lys Glu Ser Tyr Glu 35 40 45 45 act cag atg aat atg ctg tat agt cag ctt gtg gaa gca ttg agt aac Thr Gln Met Asn Met Leu Tyr Ser Gln Leu Val Glu Ala Leu Ser Asn 50 55 60 60 aac aag ggc cca gtt ttt cat gaa cat ggc tac tgg agc aag tca gat Asn Lys Gly Pro Val Phe His Glu His Gly Tyr Trp Ser Lys Ser Asp 65 70 75 80 tag 243					
Met Phe Ser Arg Ser Lys Tyr Ala Ser Ala Glu Lys Trp Cys Gly Leu 20 25 30 30 30 30 30 30 30 30 30 30 30 30 30	1	5	10	15	
Met Phe Ser Arg Ser Lys Tyr Ala Ser Ala Glu Lys Trp Cys Gly Leu 20 25 30 30 30 30 30 30 30 30 30 30 30 30 30					
gcc ttg cgt ttc ctt aac cac ctt acc tcc ttc aag gaa agc tat gaa Ala Leu Arg Phe Leu Asn His Leu Thr Ser Phe Lys Glu Ser Tyr Glu 35 40 45 act cag atg aat atg ctg tat agt cag ctt gtg gaa gca ttg agt aac Thr Gln Met Asn Met Leu Tyr Ser Gln Leu Val Glu Ala Leu Ser Asn 50 55 60 aac aag ggc cca gtt ttt cat gaa cat ggc tac tgg agc aag tca gat Asn Lys Gly Pro Val Phe His Glu His Gly Tyr Trp Ser Lys Ser Asp 65 70 75 80 tag					
gcc ttg cgt ttc ctt aac cac ctt acc tcc ttc aag gaa agc tat gaa Ala Leu Arg Phe Leu Asn His Leu Thr Ser Phe Lys Glu Ser Tyr Glu 40 45 45 45 46 45 46 45 46 45 46 45 46 45 46 45 46 45 46 45 46 45 46 45 46 45 46 45 46 45 46 45 46 45 46 46 46 46 46 46 46 46 46 46 46 46 46	Her ble Ser				Leu
Ala Leu Arg Phe Leu Asn His Leu Thr Ser Phe Lys Glu Ser Tyr Glu 35 40 45 act cag atg aat atg ctg tat agt cag ctt gtg gaa gca ttg agt aac Thr Gln Met Asn Met Leu Tyr Ser Gln Leu Val Glu Ala Leu Ser Asn 50 55 60 aac aag ggc cca gtt ttt cat gaa cat ggc tac tgg agc aag tca gat Asn Lys Gly Pro Val Phe His Glu His Gly Tyr Trp Ser Lys Ser Asp 65 70 75 80 tag 243		20	23	30	
Ala Leu Arg Phe Leu Asn His Leu Thr Ser Phe Lys Glu Ser Tyr Glu 35 40 45 act cag atg aat atg ctg tat agt cag ctt gtg gaa gca ttg agt aac Thr Gln Met Asn Met Leu Tyr Ser Gln Leu Val Glu Ala Leu Ser Asn 50 55 60 aac aag ggc cca gtt ttt cat gaa cat ggc tac tgg agc aag tca gat Asn Lys Gly Pro Val Phe His Glu His Gly Tyr Trp Ser Lys Ser Asp 65 70 75 80 tag 243	gcc ttg cgt	ttc ctt aac c	cac ctt acc tcc ttc	aag gaa agc tat	gaa 144
act cag atg aat atg ctg tat agt cag ctt gtg gaa gca ttg agt aac Thr Gln Met Asn Met Leu Tyr Ser Gln Leu Val Glu Ala Leu Ser Asn 50 55 60 aac aag ggc cca gtt ttt cat gaa cat ggc tac tgg agc aag tca gat Asn Lys Gly Pro Val Phe His Glu His Gly Tyr Trp Ser Lys Ser Asp 65 70 75 80 tag 243					
Thr Gln Met Asn Met Leu Tyr Ser Gln Leu Val Glu Ala Leu Ser Asn 50 55 60 aac aag ggc cca gtt ttt cat gaa cat ggc tac tgg agc aag tca gat Asn Lys Gly Pro Val Phe His Glu His Gly Tyr Trp Ser Lys Ser Asp 65 70 75 80 tag 243	35		40	45	
Thr Gln Met Asn Met Leu Tyr Ser Gln Leu Val Glu Ala Leu Ser Asn 50 55 60 aac aag ggc cca gtt ttt cat gaa cat ggc tac tgg agc aag tca gat Asn Lys Gly Pro Val Phe His Glu His Gly Tyr Trp Ser Lys Ser Asp 65 70 75 80 tag 243	act car ata	aat ata ota t	eat agt agg off of	+++	100
aac aag ggc cca gtt ttt cat gaa cat ggc tac tgg agc aag tca gat Asn Lys Gly Pro Val Phe His Glu His Gly Tyr Trp Ser Lys Ser Asp 65 70 75 80		-			
aac aag ggc cca gtt ttt cat gaa cat ggc tac tgg agc aag tca gat Asn Lys Gly Pro Val Phe His Glu His Gly Tyr Trp Ser Lys Ser Asp 65 70 75 80 tag 243		ASIT HEL LEG 1	-		W211
Asn Lys Gly Pro Val Phe His Glu His Gly Tyr Trp Ser Lys Ser Asp 65 70 75 80 tag 243		•	33	00	
65 70 75 80 tag 243	aac aag ggc	cca gtt ttt d	cat gaa cat ggc tac	tgg agc aag tca	gat 240
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Met	Phe	Ser	Arg 20	Ser	Lys	Tyr	Ala	Ser 25	Ala	Glu	Lys	Trp	Cys 30	Gly	Leu	
Ala	Leu	Arg 35	Phe	Leu	Asn	His	Leu 40	Thr	Ser	Phe	Lys	Glu 45	Ser	Tyr	Glu	
Thr	G1n 50	Met	Asn	Met	Leu	Tyr 55	Ser	Gln	Leu	Val	G1u 60	Ala	Leu	Ser	Asn	
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	gtt Val				-	-			-		-		-	_	•	96
	atg Met															144
	gat Asp 50												_		_	192
gtt																237

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Ala	Val	Leu	Gly 20	Ala	Cys	Ala	Ser	G1y 25	Asp.	Phe	Ala	Ser	Va1 30	Gln	Glu	
Ala	Met	A1a 35	Lys	Met	Ser	Lys	Va1 40	Gly	Lys	Val	Val	Phe 45	Pro	Arg	Leu	
G1n	Asp 50	Lys	Lys	Tyr	Tyr	Asp 55	Lys	Lys	Tyr	Gln	Va1 60	Phe	Leu	Lys	Leu	
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_	999 Gly 50							-			_			-		192
	aca Thr						-		-			-	-	gga Gly		240

65					70					75					80	
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	cct Pro										_				_	336
	ttg Leu						_	_		-				•	_	384
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net 1	His	ser.	116	5	ASP	116	116	Ald	10	rne	Leu	ıyr	Inr	11e	Leu	
He	Leu	Ala	Va1 20	Phe	Tyr	Pro	Phe	Va1 25	Asp	Leu	Ile	Asp	Asn 30	Phe	Asn	
Gln	Thr	His 35	Lys	Tyr	Ala	Pro	Phe 40	He	He	Пе	Gly	Leu 45	His	Leu	Ala	
Leu	Gly		Phe	Ser	Phe	Thr		Asp	Thr	Trp	Ser		Ser	Arg	Gly	

	50					55					60		•			
Asp 65	Thr	Ala	Glu	He	Leu 70	Gly	Ser	Gly	Ala	G1 <i>y</i> 75	Ile	Ala	Cys	Gly	Ser 80	
His	Val	Thr	Tyr	Asn 85	Met	Gly	Leu	Val	Leu 90	Asp	Pro	Ser	Leu	Asp 95	Thr	
Leu	Pro	Leu	Ala 100	Gly	Pro	Pro	Пе	Thr 105	Val	Thr	Leu	Phe	Gly 110	Lys	Ala	
Ile	Leu	Arg 115	He	Leu	He	Gly	Met 120	Val	Phe	Val	Leu	Ile 125	He	Arg	Asp	
Val	Met 130	Lys	Lys	He	Thr	Ile 135	Pro	Leu	Ala	Cys	Lys 140	Пе	Phe	Asn	He	
Pro 145	Cys	Asp	Asp	He	Arg 150	Lys	Ala	Arg	Gln	His 155	Met	Glu	Val	Glu	Leu 160	
Pro	Tyr	Arg	Tyr	11e 165	Thr	Tyr	Gly	Met	Val 170	Gly	Phe	Ser	He	Thr 175	Phe	
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aag gtg gca ggt ccc aac aag cct tgc acc acg agg aag tgg cag tgg 192 Lys Val Ala Gly Pro Asn Lys Pro Cys Thr Thr Arg Lys Trp Gln Trp 50 cat tog gga tat ggc toc otg gcc agc ttg tga 225 His Ser Gly Tyr Gly Ser Leu Ala Ser Leu * 65 70 <210> 342 <211> 74 <212> PRT <213> Homo sapiens <400> 342 Met Pro Ala Lys Asp Thr Ser Ser Val Phe Ala Leu Ala Cys Ser Pro Ala Gly Ala Pro Ser Ser Pro Gly Glu Cys Leu Gly Leu Gln Asp Arg Ile Pro His Trp Asn Arg Glu Thr Thr Tyr Phe Ser Thr Ser Leu Ser Lys Val Ala Gly Pro Asn Lys Pro Cys Thr Thr Arg Lys Trp Gln Trp His Ser Gly Tyr Gly Ser Leu Ala Ser Leu 65 70 <210> 343 <211> 240 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(240) <400> 343 atg tgc atc acg cac ctg gac cac aaa gac tac atc ttc ctg ctg ctc 48 Met Cys Ile Thr His Leu Asp His Lys Asp Tyr Ile Phe Leu Leu Leu 1 10 15 atc ggc ttc tgc atc ttc gcc gcg gga act gtg gct gcc tgg ctc aca 96 Ile Gly Phe Cys Ile Phe Ala Ala Gly Thr Val Ala Ala Trp Leu Thr 20 25 30

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ggt gtg tgt gct gtg ctc tac cag aac acc cgc cac aag tcg agt gaa 144 Gly Val Cys Ala Val Leu Tyr Gln Asn Thr Arg His Lys Ser Ser Glu 35 gaa gat gag gac gag gcc ggg act agg gtg gaa gtc agc cgg cgg att 192 Glu Asp Glu Asp Glu Ala Gly Thr Arg Val Glu Val Ser Arg Arg Ile 50 55 ttt caa acc cag acg agc tcg gtc cag gag ttc cct cag ctt att tag 240 Phe Gln Thr Gln Thr Ser Ser Val Gln Glu Phe Pro Gln Leu Ile * 65 70 75 <210> 344 <211> 79 <212> PRT <213> Homo sapiens <400> 344 Met Cys Ile Thr His Leu Asp His Lys Asp Tyr Ile Phe Leu Leu Leu Ile Gly Phe Cys Ile Phe Ala Ala Gly Thr Val Ala Ala Trp Leu Thr Gly Val Cys Ala Val Leu Tyr Gln Asn Thr Arg His Lys Ser Ser Glu 40 Glu Asp Glu Asp Glu Ala Gly Thr Arg Val Glu Val Ser Arg Arg Ile Phe Gln Thr Gln Thr Ser Ser Val Gln Glu Phe Pro Gln Leu Ile 65 70 75 <210> 345 <211> 285 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(285) <400> 345 atg act gcc aag gac tgc tcc atc atg att gca ctg tct ccc tgt ctg 48 Met Thr Ala Lys Asp Cys Ser Ile Met Ile Ala Leu Ser Pro Cys Leu 1 5 10 15

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				gtg Val		 _	-		-		_		144
				cag G1n									192
	_		_	cgt Arg 70	_			-		-	_		 240
_	-	-	-	gat Asp	_		-			_		taa *	285

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<211> 94

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<213> Homo sapiens

<400> 346

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 Gln Asp Ala Ser Ser Asp Gln Arg Pro Val Val Pro Ser Ser Arg Ser 20
 25
 30

 Arg Phe Ala Phe Ser Val Ser Val Leu Asp Leu Asp Leu Lys Pro Tyr 35
 40
 45

 Glu Ser Ile Pro His Gln Tyr Lys Leu Asp Gly Lys Ile Val Asn Tyr 50
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 60

 Tyr Ser Lys Thr Val Arg Ala Lys Asp Asn Ala Val Met Ser Thr Arg 65
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 75
 80

 Phe Lys Glu Ser Glu Asp Cys Thr Leu Val Leu His Lys Val

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<211> 474

<212> DNA

<213> Homo sapiens

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15

495

145 150 155 <210> 348 <211> 157 <212> PRT <213> Homo sapiens <400> 348 Met Glu Ala Leu Arg Arg Ala His Glu Val Ala Leu Arg Leu Leu Leu Cys Arg Pro Trp Ala Ser Arg Ala Ala Ala Arg Pro Lys Pro Ser Ala 25 Ser Glu Val Leu Thr Arg His Leu Leu Gln Arg Arg Leu Pro His Trp 40 Thr Ser Phe Cys Val Pro Tyr Ser Ala Val Arg Asn Asp Gln Phe Gly Leu Ser His Phe Asn Trp Pro Val Gln Gly Ala Asn Tyr His Val Leu Arg Thr Gly Cys Phe Pro Phe Ile Lys Tyr His Cys Ser Lys Ala Pro Trp Gln Asp Leu Ala Arg Gln Asn Arg Phe Phe Thr Ala Leu Lys Val 105 Val Asn Leu Gly Ile Pro Thr Leu Leu Tyr Gly Leu Gly Ser Trp Leu 120 125 Phe Ala Arg Val Thr Glu Thr Val His Thr Ser Tyr Gly Pro Ile Thr 135 Val Tyr Phe Leu Asn Lys Glu Asp Glu Gly Ala Met Tyr 150 155 <210> 349 <211> 288 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(288) <400> 349 atg gcg aaa gca ctg att gtc att ttt agc agt cac tta agg cct ata Met Ala Lys Ala Leu Ile Val Ile Phe Ser Ser His Leu Arg Pro Ile

10

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		ggt aaa atg gtg Gly Lys Met Val 45	
	Ile Cys Pro Val	gat gag tgg aac Asp Glu Trp Asn 60	
		gct gta cag aca Ala Val Gln Thr	
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<210> 350

<211> 95

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<213> Homo sapiens

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Met Cys Ser Ile Pro Arg His Leu Leu Pro Leu Val Leu Pro Val Ala 1 5 10 15 Leu Leu Leu Cys Ala Leu Glu Pro Leu Lys His Arg Gly Leu Glu Arg 20 25 30 Leu Ile Arg His Pro Gln His Leu Glu Arg Gly Leu Ala His Lys Thr 35 40 45

Ala Met Asn Gly Gln Pro 50

<210> 353

<211> 159

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	4ggtGly		atg													48
	tta Leu															96
	atg Met							_				_				144
-	cta Leu 50	-	-		_	-	_		_		-			•		192
	gaa Glu			-	tag *											210
	<2 <2	210> 211> 212> 213>	69	o sap	oiens	5		٠	•							
Mot		100>		Acn	llia	۸	Thu	A = 1=	T		Dh.a	C1	V-1	C1	C	
1	Gly			5					10					15		
Gly	Leu	Ile	Va1 20	Val	Ala	Tyr	Lys	Asp 25	Gly	Ser	Pro	Ala	His 30	Pro	His	
Phe	Met	Asp 35	Ala	Glu	Leu	Cys	Ser 40	Gln	Tyr	Trp	Thr	Lys 45	Trp	Leu	Leu	
Arg	Leu 50	Glu	Glu	Tyr	Thr	Glu 55		Lys	Lys	Asn	G1n 60		He	Gln	Lys	
Pro 65	Glu	Tyr	Ser	Glu							00	٠.				
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Met Val Leu Pro Val Ala Ala Tyr Xaa Leu Ile Leu Met Ala Met Leu
                  5
                                      10
                                                          15
tgg cgc ggc ctg gcc cag ggc ggg agt gcc ggc tgg ggc gcg ctg ctc
                                                                        96
Trp Arg Gly Leu Ala Gln Gly Gly Ser Ala Gly Trp Gly Ala Leu Leu
              20
                                  25
ttc acg ctc tct gat ggc gtg ctg gcc tgg gac acc ttc gcc cag ccc
                                                                       144
Phe Thr Leu Ser Asp Gly Val Leu Ala Trp Asp Thr Phe Ala Gln Pro
         35
ctg ccc cat gcc cgc ctg gtg atc atg acc acc tac tat gct gcc cag
                                                                       192
Leu Pro His Ala Arg Leu Val Ile Met Thr Thr Tyr Tyr Ala Ala Gln
     50
                          55
                                              60
ctc ctc atc aca ctg tca gcc ctc agg agc ccg gtg ccc aag act gac
                                                                       240
Leu Leu Ile Thr Leu Ser Ala Leu Arg Ser Pro Val Pro Lys Thr Asp
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tga
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Trp	Arg	Gly	Leu 20	Ala	Gln	Gly	Gly	Ser 25	Aļa	Gly	Trp	Gly	A1a 30	Leu	Leu	
Phe	Thr	Leu 35	Ser	Asp	Gly	Val	Leu 40	Ala	Trp	Asp	Thr	Phe 45	Ala	Gln	Pro	
Leu	Pro 50	His	Ala	Arg	Leu	Va1 55	Пе	Met	Thr	Thr	Tyr 60	Tyr	Ala,	Ala	Gln	
Leu 65	Leu	Ile	Thr	Leu	Ser 70	Ala	Leu	Arg	Ser	Pro 75	Val	Pro	Lys	Thr	Asp 80	
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-	aag Lys	_		_					-	_	_	-				48
	gca Ala		-	-	-	-	_	_	-		_				-	96
	ccg Pro	-	Thr	Met	Lys		Asp	Glu	Glu	Val	Met	Ala	Phe	_		144
	cga Arg 50						-									192
	gcc Ala				-	_		-								240
agt.	t.aa	aca	gga	aga	ctc	att.	cta	agt.	ata	gat.	ggc	tct	gga	ttt	tat	288

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Ser Trp Ala Gly Arg Leu Ile Leu Ser Val Asp Gly Ser Gly Phe Cys
                 85
                                     90
                                                         95
gag agg gtg aaa tot ttg gto gtt aaa caa tto tag
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Glu Arg Val Lys Ser Leu Val Val Lys Gln Phe *
            100
                                105
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      <211> 107
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Pro Ala Ser Ser Ala Arg Asp Leu Pro Ser Pro Arg Gly Tyr Thr Met
                                25
Thr Pro Gln Thr Met Lys Val Asp Glu Glu Val Met Ala Phe Arg Gly
                            40
Ala Arg Cys Asp Gly Ile Arg Val Leu Pro Ser Ser Val, Glu Asp Thr
                        55
Pro Ala Leu Lys Arg Ala Lys Ser Ser Lys Thr Gln Pro Thr Gly Asp
                    70
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Ser Trp Ala Gly Arg Leu Ile Leu Ser Val Asp Gly Ser Gly Phe Cys
Glu Arg Val Lys Ser Leu Val Val Lys Gln Phe
            100
                                105
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      <211> 252
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      <220>
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Met Glu Glu Gly Gly Gly Val Arg Ser Leu Val Pro Gly Gly Pro
1
                 5
                                     10
gtg tta ctg gtc ctc tgc ggc ctc ctg gag gcg tcc ggc ggc ggc cga
                                                                      96
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Val	Leu	Leu	Va1 20	Leu	Cys	Gly	Leu	Leu 25	Glu	Ala	Ser	Gly	Gly 30	Gly	Arg	
					-	-	_				cga Arg	-				144
											tta Leu 60					192
		_		_			-			-	aaa Lys					240
	aaa Lys	aac Asn	taa *													252
	<2 <2 <2	210> 211> 212> 213>	83 PRT Homo	sap	oiens	5										
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1	Giu	aiu	uij	5	uij	uij	vai	Al g	10	LCU	vai	110	uıy	15	110	
Val	Leu	Leu	Val 20	Leu	Cys	Gly	Leu	Leu 25	Glu	Ala	Ser	Gly	G1 <u>y</u> 30	Gly	Arg	
Ala	Leu	Pro 35	Gln	Leu	Ser	Asp	Asp 40		Pro	Phe	Arg	Va1 45		Trp	Pro	
Gly	Thr 50		Phe	Ser	Leu	Pro 55		Thr	Gly	Val	Leu 60		Lys	Glu	Asp	
Asn 65	Tyr	Val	Пе	Met	Thr 70	Thr	Ala	His	Lys	G1u 75	Lys	Tyr	Lys	Lys	Lys 80	
Lys	Lys	Asn														
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<211> 459

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<213> Homo sapiens

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					aaa Lys				-				96
					atc Ile	_	-	_				_	144
					gca Ala 55								192
					gtt Val								240
					ttg Leu								288
					tct Ser				-	_	-		336
					cag Gln								384
					gct Ala 135								432
					tgt Cys	-	tag *						459

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Phe	Gly	Leu	Ser 20	Leu	Val	Tyr	Phe	Leu 25	Ser	Ser	Thr	Phe	Lys 30	Gln	Glu	
	agg Arg															144
	ccc Pro 50															192
	agc Ser										_				•	240
	gaa Glu															288
	tgt Cys															336
	tgg Trp															384
	ctg Leu 130															432
	gcc Ala												-			480
	ttg Leu															528
	aac Asn															576
ccg	ссс	gag	ctc	ttc	ссс	gct	tga									600

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Pro Pro Glu Leu Phe Pro Ala *
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Phe Gly Leu Ser Leu Val Tyr Phe Leu Ser Ser Thr Phe Lys Gln Glu
Glu Arg Ala Val Arg Asp Arg Asn Leu Leu Gln Val His Asp His Asn
Gln Pro Ile Pro Trp Lys Val Gln Phe Asn Leu Gly Asn Ser Ser Arg
Pro Ser Asn Gln Cys Arg Asn Ser Ile Gln Gly Lys His Leu Ile Thr
                                        75
Asp Glu Leu Gly Tyr Val Cys Glu Arg Lys Asp Leu Leu Val Asn Gly
                                    90
Cys Cys Asn Val Asn Val Pro Ser Thr Lys Gln Tyr Cys Cys Asp Gly
                                105
Cys Trp Pro Asn Gly Cys Cys Ser Ala Tyr Glu Tyr Cys Val Ser Cys
                            120
Cys Leu Gln Pro Asn Lys Gln Leu Leu Leu Glu Arg Phe Leu Asn Arg
                        135
Ala Ala Val Ala Phe Gln Asn Leu Phe Met Ala Val Glu Asp His Phe
                    150
                                        155
Glu Leu Cys Leu Ala Lys Cys Arg Thr Ser Ser Gln Ser Val Gln His
                165
                                    170
Glu Asn Thr Tyr Arg Asp Pro Ile Ala Lys Tyr Cys Tyr Gly Glu Ser
            180
                                                    190
Pro Pro Glu Leu Phe Pro Ala
        195
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Met Ser Lys Tyr Lys His Lys Ser Ser Pro Leu Leu Pro Leu Leu Ile

1 5 10 15

ttt cat aat gtt tgc ttc agt cct gca aat aaa ccc aag atc ctg gct
Phe His Asn Val Cys Phe Ser Pro Ala Asn Lys Pro Lys Ile Leu Ala
20 25 30

aat gaa aaa gtc att act gtg ctt gct gcc tgt ctg gaa agt gag aat 144 Asn Glu Lys Val Ile Thr Val Leu Ala Ala Cys Leu Glu Ser Glu Asn 35 40 45

caa aat gct cag agg att gga gca gct gcc ctt ggc tct gat tta caa 192 Gln Asn Ala Gln Arg Ile Gly Ala Ala Leu Gly Ser Asp Leu Gln 50 55 60

tta tca gaa ggc aaa aac agc ttt gaa aag ccc atc agt aaa aag aag 240 Leu Ser Glu Gly Lys Asn Ser Phe Glu Lys Pro Ile Ser Lys Lys 65 70 75 80

agt gga tga 249 Ser Gly *

<210> 368

<211> 82

<212> PRT

<213> Homo sapiens

<400> 368

Met Ser Lys Tyr Lys His Lys Ser Ser Pro Leu Leu Pro Leu Leu Ile 1 5 10 15

Phe His Asn Val Cys Phe Ser Pro Ala Asn Lys Pro Lys Ile Leu Ala 20 25 30

Asn Glu Lys Val Ile Thr Val Leu Ala Ala Cys Leu Glu Ser Glu Asn 35 40 45

Gln Asn Ala Gln Arg Ile Gly Ala Ala Leu Gly Ser Asp Leu Gln 50 55 60

Leu Ser Glu Gly Lys Asn Ser Phe Glu Lys Pro Ile Ser Lys Lys 65 70 75 80

Ser Gly

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<210> 370

<211> 94

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Met 1	Asp	Gly	Arg	Gly 5	Ala	Phe	Trp	Thr	Val 10	Ala	Пе	Pro	Arg	Ala 15	Arg	
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Pro	Pro	A1 a 35	Pro	Gln	Asn	Pro	Gly 40	Gly	Ser	Thr	Gln	A1a 45	Pro	Gln	Arg	
Val	Va1 50	Gly	Lys	Ser	His	Ser 55	Gly	He	Arg	Met	Pro 60	Ala	Lys	Ser	Arg	
Asn 65	Leu	Arg	Leu	Glu	Ser 70	Lys	Leu	Asn	Arg	Thr 75	Ala	Val	Cys	Glu	A1a 80	
Leu	Lys	Arg	Ala	Pro 85	Thr	Thr	Asn	Leu	Pro 90	Gly	Val	Gly	Ser			
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				-			Asp	-	-		-		-	_		40
							cag Gln	-	_							96
							aag Lys 40									144
	-	_		-			gag G1u	_	_	_	_	_		_	•	192
							gcc Ala									240
ccg	aga	tga												•		249

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Pro Arg *
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<210> 372 <211> 82 <212> PRT <213> Homo sapiens

<400> 372

 Met
 Arg
 Asp
 Cys
 Asp
 Ile
 Asp
 Asp
 Glu
 Phe
 Leu
 His
 Leu
 Pro
 Ala

 1
 5
 10
 10
 15
 15

 His
 Leu
 Arg
 Val
 Val
 Glu
 Pro
 Glu
 Glu
 Leu
 His
 Ser
 Glu
 Thr
 Asp
 Glu
 Glu
 Ser
 Glu
 Leu
 Thr
 Asp
 Asp
 Asp
 Ala
 Leu
 Trp
 Glu
 Glu
 Glu
 Glu
 Leu
 Glu
 Lys
 Lys

<210> 373
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<400> 373

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nga gcg can gca gca ggc tcc att ccc ggc cgc cgc cgc tca gcc cat
Xaa Ala Xaa Ala Gly Ser Ile Pro Gly Arg Arg Arg Ser Ala His
20 25 30

tac gca aac ctg gcg ggt cca acc aac ccc gct ctg ccg ccg ctg ctg 144 Tyr Ala Asn Leu Ala Gly Pro Thr Asn Pro Ala Leu Pro Pro Leu Leu 35. 40 45 gaa ccc agg agg cgt gct tgc agg ctt cgg gca cta cgc ggg gct gga 192 Glu Pro Arg Arg Ala Cys Arg Leu Arg Ala Leu Arg Gly Ala Gly 50 55 aat acc acg cac tgc ccc ttc gcc tag 219 Asn Thr Thr His Cys Pro Phe Ala * 65 70 <210> 374 <211> 72 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(72) <223> Xaa = Any Amino Acid <400> 374 Met Gly Arg Ala Leu Pro Pro Gly Gly Pro Arg Arg Ala Xaa Leu 1 5 10 15 Xaa Ala Xaa Ala Ala Gly Ser Ile Pro Gly Arg Arg Arg Ser Ala His 25 Tyr Ala Asn Leu Ala Gly Pro Thr Asn Pro Ala Leu Pro Pro Leu Leu 40 Glu Pro Arg Arg Ala Cys Arg Leu Arg Ala Leu Arg Gly Ala Gly 55 60 Asn Thr Thr His Cys Pro Phe Ala 70 <210> 375 <211> 579 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(579)

										375	400>	<	
48										aag Lys			
96	-		-		-	-				gtg Val 20			
144		_		-						gct Ala			
192		-		_						gcc Åla			
240										gcc Ala			
288										aat Asn			
336										ctg Leu 100			
384										ggt Gly			
432										gtc Val			
480										gtg Val			
528										ccg Pro			

514

agc tgg gct tac tgc cgg gcc ctg cat aca cag cgc ctc cag tgg gag
Ser Trp Ala Tyr Cys Arg Ala Leu His Thr Gln Arg Leu Gln Trp Glu
180
185
170
576
579

<210> 376 <211> 192 <212> PRT

<213> Homo sapiens

<400> 376

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<210> 377 <211> 606

			DNA Homo	sap	oiens	5										
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1		Vai	um	5	LCU	vai	Aid	Aiu	10	V U I	Leu	Vai	Ala	15	vai	
						gtg Val										96
						cgc Arg										144
						acc Thr 55				_	_			_	-	192
						cat His										240
						gag G1u					-		-	-		288
						aac Asn										336
						ctg Leu										384
						gag Glu 135					-	-			_	432

	agt Ser															480
	tac Tyr															528
	ctg Leu															576
	999 Gly								-							606
		210> 211>														
		212>														
	<.	(13>	HOMO	sap	oiens	5										
	<1	100>	37Ω													
Met 1	Thr			Arg 5	Leu	Val	Ala	Ala	A1.a 10	Val	Leu	Val	Ala	Leu 15	Val	
	Leu 		20					25					30			
Gln	Thr	Leu 35	Glu	Asp	Gly	Arg	Arg 40	Arg	Ser	Val	Gly	Leu 45	Trp	Arg	Ser	
Cys	Trp 50	Leu	Val	Asp	Arg	Thr 55	Arg	Gly	Gly	Pro	Ser 60	Pro	Gly	Ala	Arg	
A1a 65	Gly	Gln	Val	Asp	A1a 70	His	Asp	Cys	Glu	A1a 75	Leu	Gly	Trp	Gly	Ser 80	
Glu	Ala	Ala	Gly	Phe 85	Gln	Glu	Ser	Arg	G1y 90	Thr	Val	Lys	Leu	G1n 95	Phe	
Asp	Met	Met	Arg 100	Ala	Cys	Asn	Leu	Val 105	Ala	Thr	Ala	Ala	Leu 110	Thr	Ala	
Gly	Gln	Leu 115	Thr	Phe	Leu	Leu	Gly 120	Leu	Val	Gly	Leu	Pro 125		Leu	Ser	
Pro	Asp 130	Ala	Pro	Cys	Trp	Glu 135		Ala	Met	Ala	Ala 140		Phe	Gln	Leu	
A1a 145	Ser	Phe	Val	Leu	Va1 150	He	Gly	Leu	Val	Thr 155		Tyr	Arg	Пe	Gly 160	
Pro	Tvr	Thr	Δcn	l eu	Sar	Trn	Sar	Cvc	Tur		Acn	Πo	GIV	د ۱ ۸		

				165					170					175		
Leu	Leu	Ala	Thr 180	Leu	Ala	Ala	Ala	Cys 185	Ser	Ser	Gly	Thr	Phe 190	Ser	Thr	
Arg	Gly	Arg 195	Thr	Ala	Trp	Pro	Pro 200	Gly								
	<2 <2	210> 211> 212> 213>	297 Dna	o sap	oiens	S										·
	<2	220> 221> 222>		(2	297)											
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	gnc		acg	ctg Leu 5											_	48
				aag Lys												96
				tca Ser							-		-	-		144
				agc Ser												192
				cgg Arg												240
				tac Tyr 85												288

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act ggt tag
                                                                      297
Thr Gly *
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      <211> 98
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      <213> Homo sapiens .
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Ala Leu Thr Arg Lys Lys Ala Leu Arg Ile His Ser Val Glu Gly Asp
Leu Arg Arg Lys Ser Ala Gly Gln Glu Glu Trp Ser Pro Ser Ala Pro
Ser Pro Pro Gly Ser Cys Val Gln Ala Glu Ala Ala Pro Ala Gly Leu
                        55
Cys Gly Glu Gln Arg Gly Glu Asp Cys Ala Glu Leu His Asp Tyr Phe
Asn Val Leu Ser Tyr Arg Ser Leu Gly Asn Cys Ser Phe Phe Thr Glu
                85
                                    90
Thr Gly .
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      <211> 264
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      <221> CDS
      <222> (1)...(264)
      <400> 381
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                                                                       48
Met Ala Val Leu Val Leu Arg Leu Thr Val Val Leu Gly Leu Leu Val
 1
                                                          15
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<211> 225 <212> DNA

														gac Asp			96
											-			aaa Lys			144
											-	-		ttc Phe			192
			_			_				-	-		-	gat Asp			240
-					tca Ser	_	tga *									-	264
	<2 <2	210> 211> 212> 213>	87 PRT	sap	oiens	5											
M-+		100>		V-1	1	A		TL	W-1	V - 1	1	01			v 1		
met 1	Ald	VdI	Leu	5	Leu	arg	Leu	ınr	vai 10	vai	Leu	ыу	Leu	Leu 15	vai		
Leu	Phe	Leu	Thr 20	Cys	Tyr	Ala	Asp	Asp 25	Lys	Pro	Asp	Lys	Pro 30	Asp	Asp		
Lys	Pro	Asp 35	Asp	Ser	Gly	Lys	Asp 40	Pro	Lys	Pro	Asp	Phe 45	Pro	Lys	Phe		
Leu	Ser 50	Leu	Leu	Gly	Thr	Glu 55	Пе	He	Glu	Asn	Ala 60	Val	Glu	Phe	Ile		
65					70	Ser	Thr	Gly	Phe	Met 75		Phe	Asp	Asp	Asn 80		
Glu	Gly	Lys	His	Ser 85	Ser	Lys											
	<2	210>	383														

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<210> 385
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       <212> DNA
       <213> Homo sapiens
       <220>
       <221> CDS
       <222> (1)...(288)
       <221> misc feature
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                                                                       48
Met Ala Pro Pro Xaa Ala Xaa Arg Ser Pro Met Ser Xaa Xaa Xaa
1
                                     10
                                                         15
ntg ctg ctg ctg ctg ctg ctg gcc ctg gcc ctg gcc cgg gcc
                                                                       96
Xaa Leu Leu Leu Leu Leu Ser Leu Ala Leu Leu Gly Ala Arg Ala
             20
                                 25
cgc gcc gag ccc gcc ggg agt gcc gtc ccc gcg cag agc cgc cca tgc
                                                                     144
Arg Ala Glu Pro Ala Gly Ser Ala Val Pro Ala Gln Ser Arg Pro Cys
         35
gtg gac tgc cac gcc ttc gag ttc atg cag cgc gcc ctg cag gac ctg
                                                                     192
Val Asp Cys His Ala Phe Glu Phe Met Gln Arg Ala Leu Gln Asp Leu
     50
                         55
cgg aag aca gcc tgc agc ctg gac gcg cgg acg gag acc cta ctg ctg
                                                                     240
Arg Lys Thr Ala Cys Ser Leu Asp Ala Arg Thr Glu Thr Leu Leu Leu
 65
                     70
                                         75
                                                             80
cag gca gag cgc cgt gcc ctg tgt gcc tgc tgg cca gcg ggg cac tga
                                                                     288
Gln Ala Glu Arg Arg Ala Leu Cys Ala Cys Trp Pro Ala Gly His *
                                                         95
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<210> 386

<211> 95

<212> PRT

<213> Homo sapiens

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      <400> 386
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                                     10
Xaa Leu Leu Leu Leu Leu Ser Leu Ala Leu Leu Gly Ala Arg Ala
Arg Ala Glu Pro Ala Gly Ser Ala Val Pro Ala Gln Ser Arg Pro Cys
                            40
Val Asp Cys His Ala Phe Glu Phe Met Gln Arg Ala Leu Gln Asp Leu
Arg Lys Thr Ala Cys Ser Leu Asp Ala Arg Thr Glu Thr Leu Leu Leu
                    70
                                        75
Gln Ala Glu Arg Arg Ala Leu Cys Ala Cys Trp Pro Ala Gly His
                85
      <210> 387
      <211> 351
      <212> DNA
      <213> Homo sapiens
      <220>
      <221> CDS
      <222> (1)...(351)
      <400> 387
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                                                                       48
Met Lys Gly Leu Arg Ser Leu Ala Ala Thr Thr Leu Ala Leu Phe Leu
 1
                 5
                                     10
                                                          15
gtg ttt gtt ttc ctg gga aac tcc agc tgc gct ccg cag aga ctg ttg
                                                                       96
Val Phe Val Phe Leu Gly Asn Ser Ser Cys Ala Pro Gln Arg Leu Leu
             20
                                 25
                                                      30
gag aga agg aac tgg act cct caa gct atg ctc tac ctg aaa ggg gca
                                                                      144
Glu Arg Arg Asn Trp Thr Pro Gln Ala Met Leu Tyr Leu Lys Gly Ala
         35
                             40
cag ggt cgc cgc ttc atc tcc gac cag agc cgg aga aag gac ctc tcc
                                                                      192
Gln Gly Arg Arg Phe Ile Ser Asp Gln Ser Arg Arg Lys Asp Leu Ser
```

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	50					55					60						
						aga Arg										. 24	40
						atc Ile										28	88
						ttt Phe										3:	36
	ctt Leu		tgg Trp	tga *												3!	51
	<2 <2	210> 211> 212> 213>	116	sap	oiens	5											
	</th <th>100></th> <th>388</th> <th></th>	100>	388														
Met 1				Arg 5	Ser	Leu	Ala	Ala	Thr 10	Thr	Leu	Ala	Leu	Phe 15	Leu		
			20			Asn		25					30	Leu			
Glu	Arg	Arg 35	Asn	Trp	Thr	Pro	G1n 40	Ala	Met	Leu	Tyr	Leu 45	Lys	Gly	Ala		
Gln	G1y 50	Arg	Arg	Phe	He	Ser 55	Asp	Gln	Ser	Arg	Arg 60	Lys	Asp	Leu	Ser		
Asp 65	Arg	Pro	Leu	Pro	G1u 70	Arg	Arg	Ser	Pro	Asn 75	Pro	Gln	Leu	Leu	Thr 80		
He	Pro	Glu	Ala	A1a 85	Thr	Ile	Leu	Leu	A1a 90		Leu	Gln	Lys	Ser 95			
Glu	Asp	Glu	Glu 100	Lys	Asn	Phe	Asp	G1n 105		Arg	Phe	Leu	Glu 110		Ser		
Leu	Leu	Asn 115	Trp														
		210> 211>															

<212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(318) <400> 389 atg aac ttg ggg gtc agc atg ctg agg atc ctc ttc ctc ctg gat gta 48 Met Asn Leu Gly Val Ser Met Leu Arg Ile Leu Phe Leu Leu Asp Val 1 10 gga gga gct caa gtg ctg gca aca ggc aag acc cct ggg gct gaa att 96 Gly Gly Ala Gln Val Leu Ala Thr Gly Lys Thr Pro Gly Ala Glu Ile 20 25 30 gat ttc aag tac gcc ctc atc ggg act gct gtg ggt gtc gcc ata tct 144 Asp Phe Lys Tyr Ala Leu Ile Gly Thr Ala Val Gly Val Ala Ile Ser 40 35 gct ggc ttc ctg gcc ctg aag atc tgc atg atc agg agg cac tta ttt 192 Ala Gly Phe Leu Ala Leu Lys Ile Cys Met Ile Arg Arg His Leu Phe 50 gac gac gac tot too gac otg aaa ago acg oot ggg ggo oto agt gac 240 Asp Asp Ser Ser Asp Leu Lys Ser Thr Pro Gly Gly Leu Ser Asp 65 70 75 80 acc atc ccg cta aag aag aga gcc cca agg cga aac cac aat ttc tcc 288 Thr Ile Pro Leu Lys Lys Arg Ala Pro Arg Arg Asn His Asn Phe Ser 85 90 95 aaa aga gat gca cag gtg att gag ctg tag 318 Lys Arg Asp Ala Gln Val Ile Glu Leu * 100 105 <210> 390 <211> 105

<212> PRT

<213> Homo sapiens

<400> 390

Met Asn Leu Gly Val Ser Met Leu Arg Ile Leu Phe Leu Leu Asp Val

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Gly	Gly	Ala	G1n 20	Val	Leu	Ala	Thr	Gly 25	Lys	Thr	Pro	Gly	Ala 30	Glu	Ile	
Asp	Phe	Lys 35	Tyr	Ala	Leu	He	Gly 40	Thr	Ala	Val	Gly	Va1 45	Ala	He	Ser	
Ala	Gly 50	Phe	Leu	Ala	Leu	Lys 55	He	Cys	Met	Пe	Arg 60	Arg	His	Leu	Phe	
Asp 65	Asp	Asp	Ser	Ser	Asp 70	Leu	Lys	Ser	Thr	Pro 75	Gly	Gly	Leu	Ser	Asp 80	
Thr	Ile	Pro	Leu	Lys 85	Lys	Arg	Ala	Pro	Arg 90	Arg	Asn	His	Asn	Phe 95	Ser	
Lys	Arg	Asp	Ala 100	Gln	Val	He	Glu	Leu 105								
	<'a	210> 211> 212>	150 DNA	o sap	nions											
			ПОШК	o 2al	rens	•										
		220>														
		221>														
	<'	222>	(1)	(150)											
	<	221>	mica	c fea	atura	2										
				(]		-										
				Α,Τ		G										
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											Leu					
ggc	CCC	cac	CCC	cta	atc	cac	atc	act	aaa	gaa	gta	gaa	gaa	aac	аоо	96
											Val					30
aca	caa	gat	qqc	aaq	cct	psp	aga	att	qcc	caq	ctg	acc	taa	aat	gag	144
											Leu					
gcc Ala	taa *															150

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      <213> Homo sapiens
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Gly Pro His Pro Leu Val His Ile Thr Glu Glu Val Glu Glu Asn Arg
                                25
Thr Gln Asp Gly Lys Pro Glu Arg Ile Ala Gln Leu Thr Trp Asn Glu
        35
                            40
Ala
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      <222> (1)...(294)
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                                                                       48
Met Asp Pro Glu Val Thr Leu Leu Leu Gln Cys Pro Gly Gly Gly Leu
1
                 5
                                     10
ccc cag gag cag ata cag gcc gag ctg agc ccc gcc cat gac cgt cgc
                                                                       96
Pro Gln Glu Gln Ile Gln Ala Glu Leu Ser Pro Ala His Asp Arg Arg
             20
                                 25
cca ctg cca ggt ggg gac gag gcc atc act gcc atc tgg gag acc cgg
                                                                      144
Pro Leu Pro Gly Gly Asp Glu Ala Ile Thr Ala Ile Trp Glu Thr Arg
         35
                             40
                                                  45
cta aag gcc caa ccc tgg ctc ttc gac gcc ccc aag ttc cgc ctg cac
                                                                      192
```

Leu Lys Ala Gln Pro Trp Leu Phe Asp Ala Pro Lys Phe Arg Leu His

tca gcc acc ctg gcg cct att ggc tct cgg ggg cca cag ctg ctc ctg
Ser Ala Thr Leu Ala Pro Ile Gly Ser Arg Gly Pro Gln Leu Leu Leu
65 70 75 80

cgc ctg ggc ctt act tcc tgc cga gtt cta tgt cca gtg cag cct gac
Arg Leu Gly Leu Thr Ser Cys Arg Val Leu Cys Pro Val Gln Pro Asp
85 90 95

ttc tga
Phe *

<210> 394 <211> 97 <212> PRT <213> Homo sapiens

400> 394
Met Asp Pro Glu Val Thr Leu Leu Leu Gln Cys Pro Gly Gly Gly Leu 1 5 10 15
Pro Gln Glu Gln Ile Gln Ala Glu Leu Ser Pro Ala His Asp Arg Arg 20 25 30
Pro Leu Pro Gly Gly Asp Glu Ala Ile Thr Ala Ile Trp Glu Thr Arg 35 40 45
Leu Lys Ala Gln Pro Trp Leu Phe Asp Ala Pro Lys Phe Arg Leu His 50 55 60
Ser Ala Thr Leu Ala Pro Ile Gly Ser Arg Gly Pro Gln Leu Leu Leu 65 70 75 80
Arg Leu Gly Leu Thr Ser Cys Arg Val Leu Cys Pro Val Gln Pro Asp 95

Phe

<210> 395 <211> 303 <212> DNA <213> Homo sapiens <220> <221> CDS

528

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Met Arg Gln Val Phe Gly Asp Glu Lys Lys Tyr Trp Leu Leu Pro Ile

1 5 10 15

ttt tca agt cta ggt gat ggc tgc tcc ttt cca act tgc ctt gtt aac 96 Phe Ser Ser Leu Gly Asp Gly Cys Ser Phe Pro Thr Cys Leu Val Asn 20 25 30

cag gat cct gaa caa gca tct act cct gca ggg ctg aat tcc aca gct
Gln Asp Pro Glu Gln Ala Ser Thr Pro Ala Gly Leu Asn Ser Thr Ala
35
40
45

aaa aat ctc gaa aac cat cag ttt cct gca aag cca ttg aga gag tcc
Lys Asn Leu Glu Asn His Gln Phe Pro Ala Lys Pro Leu Arg Glu Ser
50 55 60

cag agc cac ctt ctt act gat tct cag tct tgg acg gag agc agc ata
Gln Ser His Leu Leu Thr Asp Ser Gln Ser Trp Thr Glu Ser Ser Ile
65 70 75 80

aac cca gga aaa tgc aaa gct ggt atg agc aat cct gca tta acc atg
Asn Pro Gly Lys Cys Lys Ala Gly Met Ser Asn Pro Ala Leu Thr Met
85 90 95

gaa aat gag act taa Glu Asn Glu Thr * 100

<210> 396

<211> 100

<212> PRT

<213> Homo sapiens

<400> 396

Met Arg Gln Val Phe Gly Asp Glu Lys Lys Tyr Trp Leu Leu Pro Ile 1 5 10 15 Phe Ser Ser Leu Gly Asp Gly Cys Ser Phe Pro Thr Cys Leu Val Asn 20 25 30 Gln Asp Pro Glu Gln Ala Ser Thr Pro Ala Gly Leu Asn Ser Thr Ala

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Lys Asn Leu Glu Asn His Gln Phe Pro Ala Lys Pro Leu Arg Glu Ser
Gln Ser His Leu Leu Thr Asp Ser Gln Ser Trp Thr Glu Ser Ser Ile
                   70
                                      75
Asn Pro Gly Lys Cys Lys Ala Gly Met Ser Asn Pro Ala Leu Thr Met
Glu Asn Glu Thr
           100
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     <211> 141
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     <222> (1)...(141)
     <400> 397
48
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 1
                5
                                   10
                                                      15
ctc cga gcc ctg tcc atc ttc tcc ctg ttg gcc aac atc acc atg ctg
                                                                  96
Leu Arg Ala Leu Ser Ile Phe Ser Leu Leu Ala Asn Ile Thr Met Leu
            20
                               25
gtc agc ttg gtc atg atc tac cag ttc att gtt cag atc ctg tga
                                                                 141
Val Ser Leu Val Met Ile Tyr Gln Phe Ile Val Gln Ile Leu *
        35
                           40
                                              45
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     <211> 46
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     <400> 398
Met Leu Ser Phe Leu Pro Phe Leu Val Leu Leu Val Phe Ile Arg Asn
                                  10
Leu Arg Ala Leu Ser Ile Phe Ser Leu Leu Ala Asn Ile Thr Met Leu
                              25
Val Ser Leu Val Met Ile Tyr Gln Phe Ile Val Gln Ile Leu
                          40
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	<2	220> 221> 222>	CDS (1)	(3	360)									
	cag		agc			tac Tyr	-				-	_	_	48
-		_	-			agt Ser						•	•	96
						aac Asn		_	-	-		-	 _	144
						acc Thr 55								192
						gcc Ala								240
						gct Ala								288
						ttt Phe								336
	gta Val					gag Glu	tga *							360

WO 01/29221

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Asn Gly Ala Met Glu His Thr Asn Ser Asn Glu Ser Asp Ser Ser Pro
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Gly Arg Ser Pro Met Gln Ala Val His Pro Val His Val Lys Glu Glu
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Pro Leu Asp Pro Glu Glu Ala Glu Gly Pro Leu Ser Leu Val Thr Thr
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Ala Asn His Ser Pro Asp Phe Asp His Asp Arg Asp Tyr Glu Asp Glu
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Pro Val Asn Glu Asp Met Glu
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                                     10
                                                         15
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Ser Leu Leu Leu Leu Val Val Cys Gly Ile Gly Cys Val Trp His
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                                 25
tgg aaa cac cgt gtt gcc aca cga ttt acc tta ccg agg ttt tta caa
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Trp Lys His Arg Val Ala Thr Arg Phe Thr Leu Pro Arg Phe Leu Gln
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						cat His										240
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						tac Tyr							tag *			474
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	Leu	Leu	Leu 20	-	Leu	Val	Val	Cys 25		He	Gly	Cys	Va1 30		His	
Trp	Lys	His 35		Val	Ala	Thr	Arg 40		Thr	Leu	Pro	Arg 45		Leu	Gln	
Arg	Arg 50		Ser	Arg	Arg	Lys 55		Cys	Thr	Lys	Thr 60		Leu	Gly	Pro	

Arg 65	Пe	He	Gly	Leu	Arg 70	His	Glu	He	Ser	Va1 75	Glu	Thr	Gln	Asp	His 80	
Lys	Ser	Ala	Val	Arg 85	Gly	Asn	Asn	Thr	His 90	Asp	Asn	Tyr	Glu	Asn 95	۷a۱	
			100					105			Asp	-	110		-	
		115	•				120				He	125				
	130					135					Arg 140		Ser	Glu	Val	
Pro 145	Gln	Asp	Glu	Asp	11e 150	Tyr	He	Leu	Pro	Asp 155	Ser	Tyr				
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											ggt Gly					96
											gag G1u					144
											gag Glu 60					192
											cta Leu					240
aaa	act	ata	cta	aac	aga	aac	cac	cca	ดลด	ลลด	aat	taa				279

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Ile Ser Glu Arg Arg Glu Asp Arg Lys Leu Asp Glu Leu Leu Gly Lys

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cag cct aaa agg cga cgg cgg att gac aga agt atg att gga gag ccc 96 Gln Pro Lys Arg Arg Arg Ile Asp Arg Ser Met Ile Gly Glu Pro 20

aca aac ttt gtg cat aca gct cat gtt gga tca gga gac ctg ttc agt 144 Thr Asn Phe Val His Thr Ala His Val Gly Ser Gly Asp Leu Phe Ser 35

gga atg aat toa gtt ago too att cag aac caa atg cag too aag gga 192 Gly Met Asn Ser Val Ser Ser Ile Gln Asn Gln Met Gln Ser Lys Gly 50 55 ggt tat gga ggt gga atg cct gcc aat gtc cag atg cag ctc gtg gat 240 Gly Tyr Gly Gly Met Pro Ala Asn Val Gln Met Gln Leu Val Asp 65 70 80 acg aag gcg gga tag 255 Thr Lys Ala Gly * <210> 406 <211> 84 <212> PRT <213> Homo sapiens <400> 406 Met Ser Glu Phe Trp Leu Cys Phe Asn Cys Cys Ile Ala Glu Gln Pro Gln Pro Lys Arg Arg Arg Ile Asp Arg Ser Met Ile Gly Glu Pro Thr Asn Phe Val His Thr Ala His Val Gly Ser Gly Asp Leu Phe Ser 40 Gly Met Asn Ser Val Ser Ser Ile Gln Asn Gln Met Gln Ser Lys Gly 55 Gly Tyr Gly Gly Met Pro Ala Asn Val Gln Met Gln Leu Val Asp 70 75 80 Thr Lys Ala Gly <210> 407 <211> 249 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(249) <400> 407

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											tta Leu 60					192
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	agc Ser	tga *														249
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Arg	Ile	Leu 35		Thr	Gly	Leu	Asp 40		Glu	Thr	Leu	Ser 45		Cys	Val	
Arg	Leu 50		Glu	Gln	Gly	Ile 55		Pro	Glu	Ala	Leu 60		Ser	Val	Пе	
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Thr Ser

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                                                          15
ctc ctg ggt gct gcc aca gag aag aga gag aga gtg aag cgg gca gag
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Leu Leu Gly Ala Ala Thr Glu Lys Arg Glu Arg Val Lys Arg Ala Glu
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                                 25
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act ggc tgt tgc cat cac aca act gag ggc gga cct gga gct cac cgg
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Thr Gly Cys Cys His His Thr Thr Glu Gly Gly Pro Gly Ala His Arg
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Leu Arg Val *
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				ttc Phe										240
	_			anc Xaa 85										288
				ttc Phe										336
				atc Ile										384
gcg	ttg	сас	atc	cta	aag	ttt	gaa	gag	tct	aaa	taa			420

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Val Met Arg Gly Thr Arg Cys Leu Ala Glu Tyr His Leu Gly Asp Tyr
Gly His Ala Trp Asn Arg Cys Trp Val Leu Asp Arg Val Asp Thr Trp
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Ala Val Val Met Phe Ile Asp Phe Gly Gln Leu Ala Thr Ile Pro Val
Gln Ser Leu Arg Xaa Xaa Asp Ser Asp Asp Phe Trp Thr Ile Pro Pro
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                                    90
Leu Thr Gln Pro Phe Met Leu Glu Lys Asp Ile Leu Ser Ser Tyr Glu
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						gaa G1u			240
						tcc Ser		•	288
					-	tcc Ser	 	_	336
						agt Ser			384
						cgg Arg 140			432
						aag Lys			480
						ata Ile			528

	tgt Cys														_	576
	agc Ser														-	624
	gaa Glu 210															672
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Thr	Asp 50		Leu	Val	Pro	Met 55		Gly	Asn	Asn	Pro 60		Ala	Thr	Thr	
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Glu	Glu	Met	Glu	Lys 165	Ser	Arg	Cys	He	Pro 170	Glu	He	Asp	Asp	Ser 175	Glu	
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Ser	Glu 210	Gly	Asp	Asn	Пe	Pro 215	Asp	Ala	Leu	Gly	Leu 220	Val	Glu	Tyr	Leu	
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	ctc Leu															96
	atg Met	-	-				-	_	-			-	-	-		144

543

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	gag G1u															144
	cat His 50															192
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	tca Ser															336
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Lys	Glu	Leu 35		Glu	Lys	Gln	Pro 40		Leu	Ser	Phe	G1y 45		Ala	Ile	
Leu	His 50		Phe	Ser	Ala	Asp 55		Lys	Lys	Val	Gly 60		Lys	Leu	Leu	
Gln	Glu	Пe	Asn	Lys	Gly		Пe	Asp	Ala	Val		Ser	Leu	Met	He	

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Leu	Arg	Ser 115	Gln	Ala	Ala	Val	Thr 120	Glu	Ile	Ser	Glu	Glu 125	Asp	Asp	Ala	
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			atg Met													192
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			cag													240
65 65	Lys	Lys	Gln	uIII	70	นเน	um	116	cys	75	ыу	ыу	ser	ser	Ser 80	
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val	met	5er	Leu	A1a 85	Ihr	Lys	met	Asn	Glu 90	Leu	Met	Glu	Lys	*		

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	Asp	Val	His 20		Gly	Phe	Leu	Ser 25		Arg	Leu	Arg	A1a 30		Gln	
Pro	Leu	Thr 35	Gly	Trp	Ser	Cys	Glu 40	Thr	Pro	Arg	Ser	G1y 45	Met	Leu	Leu	
Gln	Va1 50	Val	Met	Ala	Val	Ala 55	Asp	Thr	Ser	Ala	Lys 60	Ala	Val	Glu	Thr	
Va1 65	.L y s	Lys	Gln	Gln	G1 y 70	Glu	G1n	Пe	Cys	Trp 75	Gly	Gly	Ser	Ser	Ser 80	
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